New Catalysts and New Substrates in Ring-Closing Metathesis

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Foreword

This PhD thesis, except for Chapter 1, is based on the results published or going to be published in international scientific journals. Chapters 2, 3 and 4 correspond to the papers in as much unchanged form of the respective manuscripts as possible. Therefore, compounds and references are numbered independently in each chapter.

Zusammenfassung

In den letzten 20 Jahren entwickelte sich die Olefin-Metathese zu einer ausgezeichneten Methode um Kohlenstoff-Kohlenstoff Doppelbindungen zu manipulieren. Trotz des ernormen Fortschritts bezüglich Stabilität von Katalysatoren, deren hohe Aktivitäten und deren Toleranz gegenüber funktionellen Gruppen sind weitere Verbesserungen von grosser Bedeutung. Diese Dissertation ist dem Ziel gewidmet neuartige Katalysatoren zu synthetisieren und deren Verhalten in der Ringschlussmethatese (RCM) zu untersuchen.

Der erste Abschnitt dieser Arbeit, welcher im zweiten Kapitel beschrieben ist, konzentriert sich auf die Entwicklung von einer Reihe auf Ruthenium basierende Metathesekatalysatoren der Hoveyda-Blechert-Familie. Diese Katalysatoren bestehen aus *N*-heterozyklische Carbene mit einer substituierten Naphthyl-Seitenkette. Zum ersten Mal war eine chromatographische Trennung und Aufreinigung der *syn*- und *anti*-Isomere einiger Katalysatoren erfolgreich.

Durch verschiedene kinetische Untersuchungsreihen an den isolierten Isomeren konnten entscheidende Unterschiede in der Aktivität und Stabilität zwischen *anti*- und *syn*-Konformeren des Katalysators festgestellt werden.

Intensive Studien zur Auswirkung der Konzentration auf die Reaktionsrate von RCM-Reaktionen wurden zusätzlich durchgeführt mit dem Ergebnis, dass unter bestimmten Konditionen, sehr hohe Konzentrationen des Vorläufer-Diens zu RCM führen kann mit einer Vielfalt von Substraten mit extrem niedrig katalytischer Ladung.

Im dritten Kapitel wird die Synthese und Charakterisierung einer neuen Familie von NHC mit mono- oder disubstituierten Seitenketten behandelt. Das Ziel dieser Arbeit war das Erlangen von Liganden, welche vorwiegend die *anti* –Konformation einnehmen. Dadurch wird erreicht, dass diese Komponenten vielseitiger in der Organischen Chemie und als Organokatalysatoren einsetzbar sind. Insbesonders können durch Inkorporation der Liganden diese Ru-Katalysatoren zu Metathese-Reaktionen verwendet werden.

Im vierten Kapitel wird zum Abschluss die Entwicklung jener katalytischen Methoden, um Alkenbromide durch RCM-Reaktionen zu erhalten, angestrebt. Dafür

werden katalytische Mengen von kommerziell erwerblichen Katalysatoren verwendet. Diese Produkte stellen ein grosses Interesse, nicht nur als Bausteine in der Organischen Synthese dar, sondern auch als Möglichkeit neuwertige milde synthetische Wege einzuschlagen. Eingeschlagene Versuche diese Reaktionsmechanismen zu klären werden in dieser Arbeit vorgestellt.

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CHAPTER ONE

1.1 Introduction to olefin metathesis

In the last 50 years olefin metathesis (OM) experienced an amazing evolution becoming one of the most useful synthetic transformation for generating carbon-carbon double bonds.[1,2,3,4] This metal catalyzed reaction involves two olefins that, *via* a metallacyclobutane intermediate, undergo a disproportionation (Figure 1).

Figure 1. Olefin metathesis reaction

This reaction can be applied in a great variety of synthetically useful permutations, including ring-closing metathesis (RCM), cross metathesis (CM), enyne metathesis, acyclic diene metathesis polymerization (ADMET) and ring-opening metathesis polymerization (ROMP) (Figure 2). A huge number of catalysts has been developed and tested for these transformations; however, ruthenium alkylidene complexes have become the most widely used in organic synthesis.

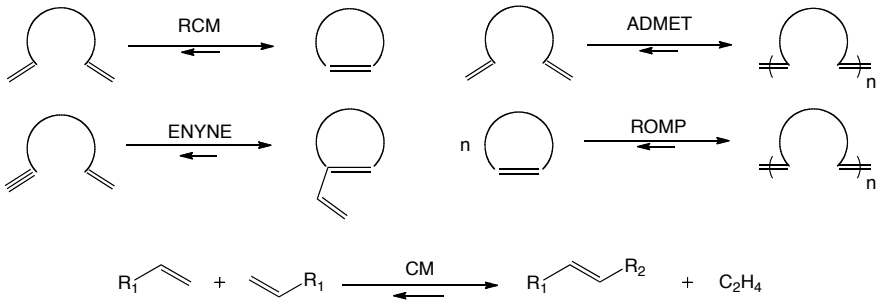
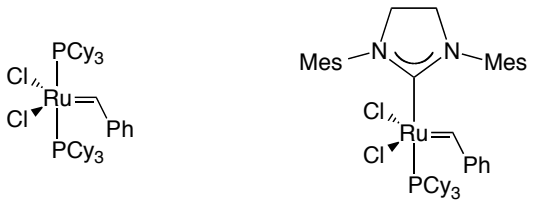


Figure 2. Some of the most commonly used olefin metathesis transformations.

The success is mostly due to their excellent functional group tolerance combined with a high activity and remarkable stability toward air and moisture.[1,2] The

commercial availability of some of these catalysts, mainly Grubbs first and second-generation (Figure 3), also played a key role in their rapid diffusion.



Grubbs I generation (GI) Grubbs II generation (GII)

Figure 3. Grubbs first and second-generation catalysts.

In the past few years, the application of ruthenium-based olefin metathesis catalysts has expanded to include the synthesis of molecules in organic, inorganic, biochemical, polymer, and materials chemistry.[5] Quite a few studies on large-scale application were also developed but none has yet been implemented.[6]

1.2 Nature and reactivity of carbenes

In order to understand how an olefin metathesis catalyst works, it is important to study the nature of a carbene and its reactivity toward a metal center. Carbenes are neutral species containing a carbon atom with only six valence electrons. They are, in most of the cases, too reactive to be isolated and observed. Spectroscopic investigations of a number of carbenes of different structures have shown that they fall broadly into two groups: those that electron spin resonance spectroscopy (ESR) demonstrates have unpaired electrons and whose bond angles are between 130 and 150°; and those that have bond angles of 100-110° but cannot be observed by ESR. The first are generally called triplet state carbene; the second are referred to as singlet state carbene. Many carbenes, like $:CH_2$, can be found in either states (Figure 4).

The bond angle between 100 and 150°, observed for most of the carbenes, suggests a trigonal (sp^2) hybridization state. An sp^2 hybridized carbene would have three, lower energy, sp^2 orbitals and one, higher energy, p orbital in which to distribute its six electrons. There are two possible ways to do this.

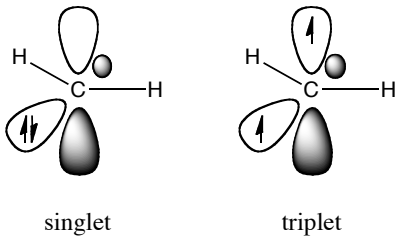


Figure 4. Representation of singlet and triplet state carbenes.

Either all of the electrons can be paired, with each pair occupying one of the sp^2 orbitals, or two of the electrons can remain unpaired, with one electron in the p orbitals and one in the remaining sp^2 orbital (Figure 5). These two possibilities explain the existence of the two observed classes of carbenes.

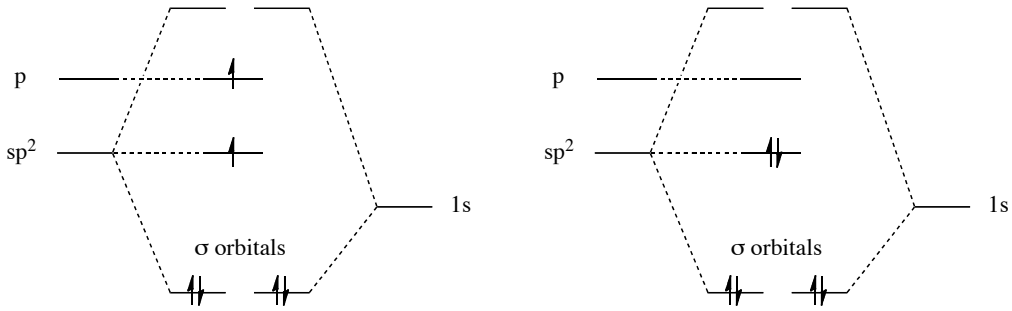


Figure 5. Electronic structure of an sp^2 hybridized carbene with 2 unpaired electrons (left) and two paired electrons (right).

The existence of the two spin states explains the different behavior of triplet and singlet carbenes in ESR spectroscopy.

Most of the carbenes are more stable in the triplet state because the energy to be gained by bringing the electron in the p orbital down into the sp^2 orbital is insufficient to overcome the repulsion that exists between two electrons in a single orbital.

Carbenes can be considered, in some aspects, as extremely reactive Lewis acids. This explains why they are able to react with very weak Lewis bases, like unactivated olefins or even simple alkanes (Figure 6). These reactions can be considered as

insertion reactions and, depending on the state of the carbene, can proceed with a concerted cycloaddition or a radical mechanism. [7,8]

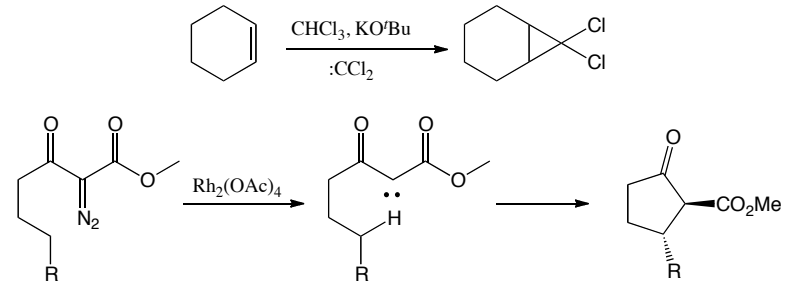


Figure 6. Two examples of reactions of carbene in organic synthesis.

In all the cases in which the singlet state is the lower energy state, an electron-rich substituent carrying lone pairs is present adjacent to the carbene center. These lone pairs can interact with the p orbital of the carbene to produce a new, lower-energy orbital which can be occupied by the two electrons. This type of molecule is normally less electrophilic than other carbenes and, in particular cases, they can be quite nucleophilic (Figure 7). [9]

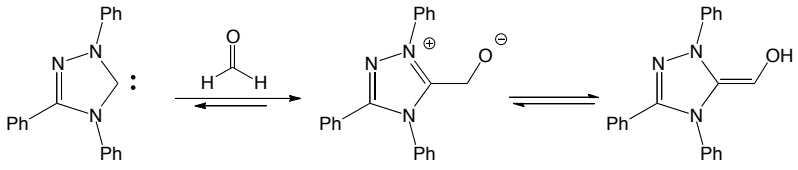


Figure 7. Reaction between a nucleophilic carbene and formaldehyde.

1.3 Interaction of carbenes with metals

The first studies on the interaction of a carbene with a metal started in the 1960s. The pioneer of this chemistry was Ernst Otto Fischer who in 1964 presented the first important work aimed to prove that some particular types of carbenes were indeed able to generate a remarkably stable bond with a transition metal.[10] His contribution

to this topic was so important that these types of carbenes nowadays are generally called Fischer carbenes (Figure 8). For this discovery and for more extensive work in the organometallic field (in particular for the discovery of Ferrocene) Fischer was awarded the Nobel prize in chemistry in 1973.

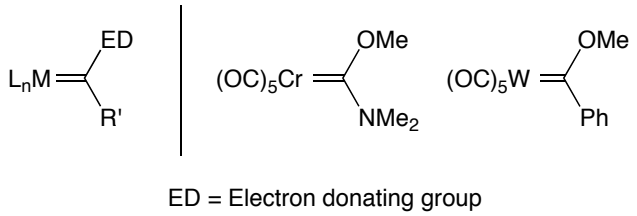


Figure 8. The general structure of a Fischer type carbene (left) and two classical examples (middle and right).

Fischer carbenes are typically found with electron-rich, low oxidation state metal complexes (middle to late transition metals) containing π-acceptor ligands (such as CO). They feature a π-donor substituent on the methylene group such as alkoxy or alkylated amino groups. Looking at the orbital interaction, two main processes take place: the σ-donation from the carbene to an empty d-orbital of the metal and the retro-donation from a filled metal orbital into an empty p-orbital of the carbon (Figure 9). There is competition between the retro-donation process and the donation of a lone pair from the heteroatom and this is consistent with the last resonance structure shown in Figure 9. This model explains, at least in part, the electrophilic-at-carbon nature of Fischer carbenes.

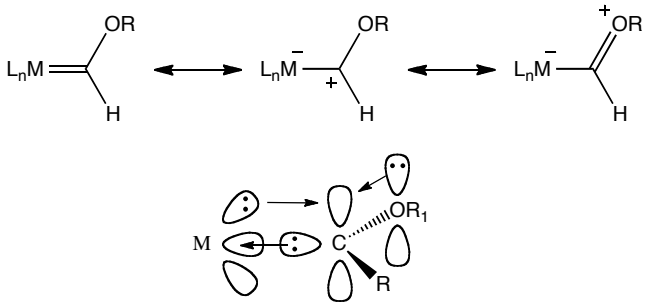


Figure 9. Resonance structures of a Fischer carbene (above) and an interpretation of a Fischer carbene-metal bond with molecular orbitals (below).

Metal complexes of Fischer carbenes have proven to be highly stable and very efficient and versatile starting material for a wide array of cycloaddition and cyclopropanation reactions.[11] However, a major limit in their application in modern organic synthesis is the necessity to employ a stoichiometric amount of reagent. Efforts to solve this problem are underway and some limited success has been achieved.[12]

Carbenes that are not stabilized with a π-donor substituent generate a totally different type of metal complexes. These species, commonly called Schrock carbenes, generally form stable complexes with electron poor, early transition metals in a high oxidation state. Bonding in such complexes can be viewed as the coupling of a triplet state metal and triplet carbene. These bonds are polarized towards carbon and therefore the methylene group presents strong nucleophilic character (Figure 10).

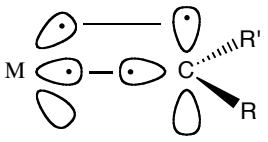


Figure 10. Interpretation of a metal-Schrock carbene bond with molecular orbital.

Schrock carbenes are widely used in organometallic chemistry and metathesis is certainly one of the most important catalytic applications.

Only in 1991, almost three decades after Fischer's discoveries, the work of Arduengo brought to the development of the first stable free carbene (Figure 11).[13]

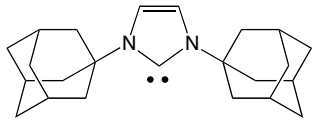


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Figure 11. The first stable free carbene developed from Arduengo.

The core of the molecule constituted an *N*-heterocycle hence its name *N*-heterocyclic carbene (NHC). This species proved to be stable in the absence of oxygen and moisture and it could be handled easily, being a crystalline solid. NHCs feature a good σ-donor character, similarly to Fischer carbenes, but their π-acceptor character

is very weak. This results in an empty p-orbital on the carbene carbon that is partially stabilized by the lone pairs of the adjacent heteroatoms. As a result, the interaction between the metal and the NHC is usually represented as a single bond with a delocalized charge on the heterocyclic ring (Figure 12).

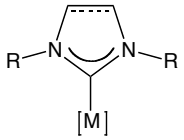


Figure 12. Classical representation of a metal-NHC bond.

After the discovery of Arduengo, NHCs started to attract a great interest as ligands in organometallic chemistry. Thanks to the pioneering work of Herrmann, followed by Grubbs, Nolan and many others, they now represent, in many applications, a valid alternative to tertiary phosphine. The main advantage, with respect to the classical phosphine ligands, consists in the greater stability towards heat, oxygen and moisture observed for NHC complexes.[14]

Despite the great effort spent in the last decade, to date only a few types of NHCs are commercially available and largely employed in common organometallic chemistry. They are aryl-substituted imidazol-2-ylidenes (2,4,6-mesityl-substituted IMes and 2,6-isopropylphenyl-substituted IPr) and their saturated imidazolin-2-ylidene counterparts (SIMes and SIPr) (Figure 13). In Chapter 3 some of the results obtained in the last years in our group concerning the development of new NHCs that feature naphthyl-substituted side chains will be presented.

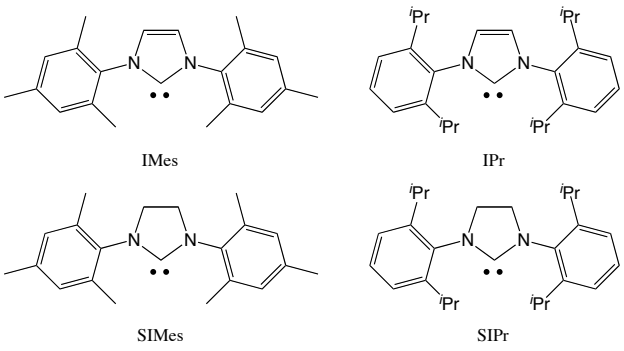


Figure 13. The most common NHCs currently used.

1.3 Mechanism of olefin metathesis

The discovery of olefin metathesis raised questions concerning the exact mechanism of this type of transformation. Initially, a number of ideas were postulated, none of which fully matched the experimental observations.[15,16,17] Only in 1971, starting from those early studies and in particular from the one developed from Calderon, Chauvin was able to propose a mechanism that appeared to be consistent with the experimental data.[18] He was the first to hypothesize that in the key step of the metathetic process an unstabilized, very reactive metal-alkylidene complex had to be involved (Figure 14).[19] In the proposed mechanism, after coordination of an olefin to the metal center (**II**) a [2+2] cycloaddition takes place, generating a metallacyclobutane (**III**). The intermediate can rapidly evolve releasing ethylene and generating a new metal alkylidene (**IV**) that can then undergo the same sequence of transformations reacting with a new olefin, eventually completing the disproportionation of two double bonds, as shown in Figure 14.

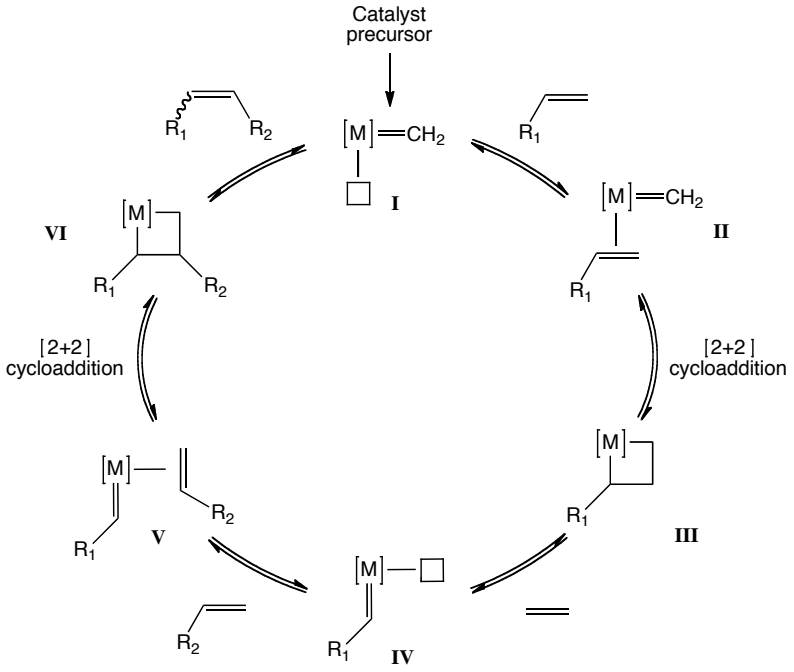


Figure 14. Proposed olefin metathesis mechanism.

All the steps of this process are reversible and only the presence of a driving force, such as the formation of volatile byproducts that can be released from the reaction environment, drive the equilibrium towards a specific product.

Today this mechanism is commonly accepted and new theoretical[20] as well as experimental[21] evidences for the involvement of these intermediates in the catalytic cycle are continuously being reported.

Less developed are the studies that aim to identify the way in which the olefin approaches the metal center. Evidence for a bottom-bound intermediate were obtained from Snapper employing Grubbs first generation (**GI**) and a strained tricyclic cyclobutene substrate (Figure 15, left).[22] Later, Grubbs, employing ortho-divinylbenzene as a test substrate and a Grubbs third generation catalyst (**GIII**), was able to prove with NMR and X-Ray crystallographic studies that, after the first cross-metathetic step in the catalytic cycle, the remaining olefin coordinates to ruthenium in a *cis* position with respect to the NHC (Figure 15, right).[21a]

A criticism that can be made of these two types of studies is associated with the use of model substrates that have a restricted conformational freedom, and therefore do not represent well, the class of substrates commonly used in olefin metathesis.

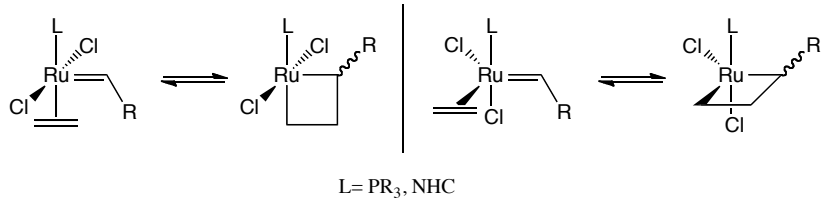
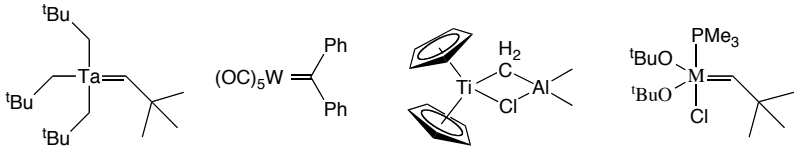


Figure 15. Side bound-intermediate (left) and bottom bound-intermediate (right).

Computational studies performed by Goddard[23] and Cavallo[20a] on Grubbs second-generation catalysts suggest that the preferred reaction pathway is governed by a delicate balance between electronic, steric and solvent effect. Polar solvents should push toward the side reaction pathway and can easily overturn an electronic preference for the bottom reaction pathway. This means that, with less bulky ligands and/or substrates, the side reaction pathway can be indeed competitive. If these prerequisites are not present, the bottom reaction pathway becomes strongly favored.

1.4 Historical evolution of olefin metathesis catalysts

Olefin metathesis was initially observed in the 1950s during the research performed on Ziegler-Natta polymerization processes.[24] In the early 1960s, industrial chemists at DuPont discovered that alumina-supported molybdenum species catalyzed the transformation of propene into 2-butenes and ethylene. Similar catalysts were also able to induce polymerization of cyclopentene and norbornene, generating completely new polymers.[25] These observations were followed by several reports describing improved catalytic systems based on molybdenum and tungsten that catalyzed either the polymerization of cyclic olefins or the disproportionation of linear olefins.[26] For more than 20 years, until the early 1970s, olefin metathesis catalysts were based on multi-component systems that consisted of early transition metal salts and alkylating reagents, generally based on aluminum. Although these systems were limited in substrate scope and required high reaction temperature, their catalytic activity was high and some important industrial application were implemented (*e.g.* the SHOP and Phillips triolefin processes).[27] Only after the hypothesis formulated from Chauvin regarding the participation in the olefin metathesis reaction of a metal alkylidene moiety a great effort was concentrated in the isolation and characterization of well-defined catalytic systems. In 1974 Schrock was able, for the first time, to isolate and characterize a tantalum complex containing a stable alkylidene (**1,** Figure 16), definitely proving the existence of this chemical entity and giving a fundamental support to the metathesis mechanism proposed by Chauvin.[28]

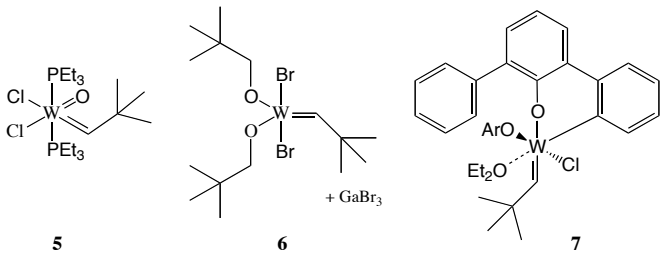


1 Schrock 1974 | **2** Katz 1975 | **3** Tebbe 1978 | **4** (M= Nb, Ta) Schrock 1980

Figure 16. Evolution of well-defined metathesis catalysts.

Two years later, in 1976, Katz reported the first well-defined metal carbene that underwent olefin metathesis. The $[(CO)_5W(=CPh_2)]$ complex **2** initiated metathesis, albeit at a low rate, of a variety of di- and tri-substituted cycloalkenes and *E*- and *Z*-2-pentenes.[29] In 1978 Tebbe et al. proposed the first homogeneous metathesis catalyst based on titanium and aluminum (**3**). Despite the low activity in metathesis some insight into the mechanism of the reaction were proposed in 1980. Using the same catalyst, Grubbs et al. were able to isolate, characterize and study the reactivity of a stable metallacyclobutane intermediate.[30] This catalyst, today called Tebbe's reagent, is still widely used for olefination reactions of esters. In the same period, Schrock and coworkers had started to investigate the behavior of high-oxidation state metal alkylidene complexes in the presence of olefins.[31] In 1980 this resulted in the development of Nb/Ta-complexes **4** that catalyzed the metathesis of *cis*-2-pentene. Formation of new alkylidene complexes upon reaction of **4** with styrene presented another solid proof for Chauvin's proposed olefin metathesis mechanism.[32]

Encouraged by the good results obtained with poorly defined, high oxidation state tungsten-based systems and by the good results of complex **2**, Schrock and other groups started to synthesize W- and Mo-alkylidene complexes and evaluate their activity as catalysts for olefin metathesis.[33] The first stable, catalytically active W-alkylidene complexes were reported throughout the 1980s by the groups of Schrock,[34] Osborn[35] and Bassett[36] (Figure 17, complex **5-7**).

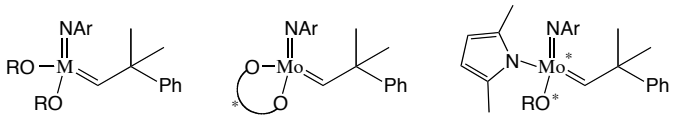


5 Schrock 1980 **6** Osborn 1983 **7** Basset 1985

Figure 17. The first well-defined W-based metathesis catalysts

Finally, in 1990, Schrock proposed a series of single-component imido-alkylidene catalysts in which two bulky, electron poor alkoxide ligands contributed to increase the stability of the complexes (Figure 18). These compounds are still

nowadays among the most active catalysts known and a wide number of modifications were developed and employed in synthetic organic chemistry.[37]



8 (M = W, Mo) Schrock 1990 | **9** Schrock 1993 | **10** Schrock-Hoveyda 2007

Figure 18. General structure of one of the most active metathesis catalysts (**8**) and of its asymmetric version (**9**, **10**).

Asymmetric versions of these catalysts were also developed in 1993 by Schrock. The first generation of chiral catalysts featured, in place of the two bulky alkoxide groups, a bidentate, C_2-symmetric chiral diolate ligand (**9,** Figure 15).[38] More recently Schrock and Hoveyda were able to synthesize a second-generation of chiral catalysts in which the chelating diolate was substituted with an enantiomerically pure aryl alcohol and a functionalized pyrrole.

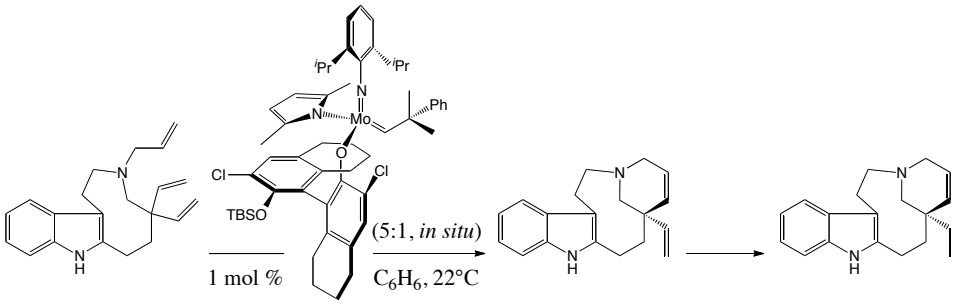


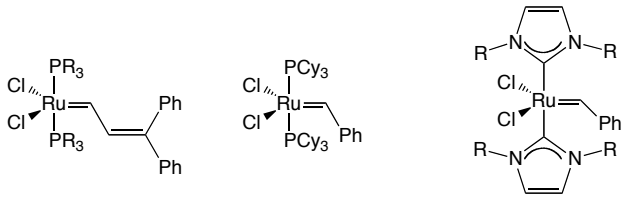
Figure 19. Asymmetric synthesis of Quebrachamine.

These complexes are stereogenic at metal and proved to be extremely active and highly stereoselective. One of the more fascinating examples of their application in synthetic organic chemistry is the enantioselective synthesis of (+)-Quebrachamine (Figure 16).[39,40]

Despite the great improvement that Schrock catalysts experienced in the last decade, their high sensitivity to moisture and air, along with the complexity of their synthesis, are still major drawbacks.

In parallel with the discovery and evolution of tungsten and molybdenum based catalysts, Grubbs explored the chemistry of ruthenium alkylidene based complexes. The first successful results were achieved, in terms of catalyst activity and stability, in 1992 with the discovery of complex **11** (Figure 17). Although the activity of **11** was poor with respect to the Mo-based catalysts, it was significantly more versatile due to its remarkable functional group tolerance. In addition, it was not very air sensitive as a solid and displayed a good resistant to water, alcohols and acids.[41] The synthesis of this complex though was still particularly difficult. In this sense a great advancement was achieved with the discovery of catalyst **12**, today known as Grubbs first generation catalyst: not only was this catalyst around 20,000 time more active than **11,** but it could also be easily obtained via a short, high yielding synthetic pathway. Remarkably, the necessity to use potentially explosive diazo-compounds during the synthesis of this compound did not hamper the development of large scale processes and nowadays it can be produced in multi-kilogram scale.[42]

After only three years from the discovery of **12**, a new, revolutionary, advance was achieved in the Herrmann group. He was able, for the fist time, to replace the two phosphines present in complex **12** with imidazolin-2-ylidene ligands generating a completely new class of catalysts. Although these complexes showed little, if any, improvements in applications to ROMP and RCM,[43] they opened the way to the use of NHCs as ligands not only for olefin metathesis catalysts but for a large plethora of other catalysts that today are key instruments in modern organic chemistry.



11
Grubbs
1992

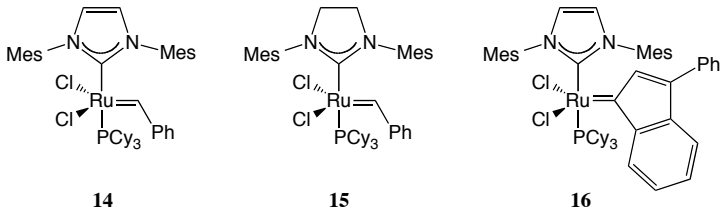
12
Grubbs
1995

13
Herrmann
1998

Figure 20. Some of the first Ru-based metathesis catalysts.

In 1999 Grubbs[43,44] and Nolan[45] were able to displace selectively only one phosphine from complex **12** using IMes and SIMes. These new catalysts (**14** and **15**, figure 18) were slightly less reactive than **12** at room temperature in ring-closing metathesis reactions but at higher temperatures the reactivity increased dramatically. In addition, complex **15** exhibited increased ring-closing activity towards sterically demanding substrates, being able to generate in moderate to excellent yield tri- and tetra-substituted olefins.

As an alternative to Ru-benzylidene catalysts, NHC bearing Ru-3-phenylindenylidene complexes,[46] such as **16**, were developed and are now widely used in natural product synthesis (Figure 21).[47] The Ru-indenylidene complexes showed a higher thermal stability than their benzylidene counterparts and, at the same time, showed a good catalytic activity and selectivity. It is important to note that these complexes can be obtained using a simple and high yielding procedure that avoids the use of diazo-compounds.



14
Grubbs-Nolan-Herrmann
1999

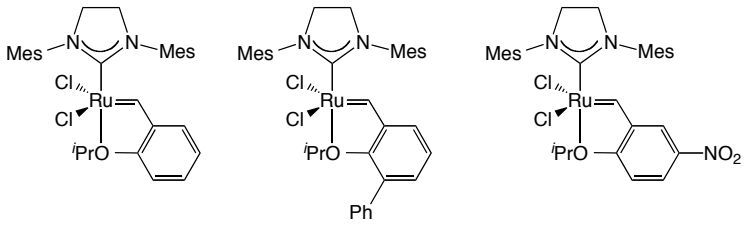
15
Nolan
1999

16
Grubbs
1999

Figure 21. Ru-based metathesis catalysts containing one phosphine.

In 2000 Hoveyda[48] and Blechert[49] developed, in parallel, the first phosphine-free ruthenium-based metathesis catalyst. Starting from the second-generation Grubbs catalyst they were able to introduce a chelating benzylidene ligand generating complex **17** (Figure 21). This catalyst was found to be particularly stable but less active, generally requiring high temperature to be activated. This problem was partially solved in 2002 by Blechert and Grela. The first introduced a phenyl ring in position α to the isopropoxy group of **17**, generating a strong steric repulsion that facilitates the dissociation of the ether moiety from the metal center (**18**, Figure 22);[50] the second introduced a strongly electron-withdrawing group on the benzylidene ring

of **17**, reducing the propensity of the ether moiety to bind to the metal center (**19**, Figure 22).[51] In both cases, the catalysts became active at room temperature.



17
Hoveyda
2000

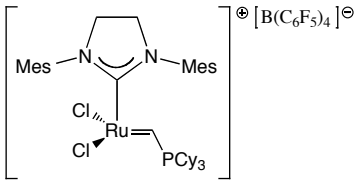
18
Blechert
2002

19
Grela
2002

Figure 22. Ru-based metathesis catalysts containing a chelating benzylidene.

Another important attempt to induce faster activation of second-generation Grubbs-type catalyst was performed by the group of Piers. He was able to isolate a stable pre-catalyst containing a 14-electron metal center (**20**, Figure 23). This compound, now commercially available, has been used mainly to perform mechanistic studies at very low temperature, conditions under which conventional catalysts would be too unreactive.[52]

Many other modifications of the catalysts were performed but their impact was not as relevant as the one previously reported. Great effort was also spent, with modest success, in generating complexes immobilized on different solid support, in order to obtain a recyclable catalyst that could be more easily used in industrial applications.[53]



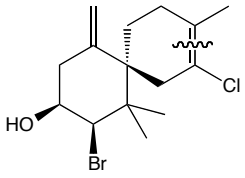
20
Piers
2004

Figure 23. One of the more successful examples of fast activating Ru-based olefin metathesis catalysts.

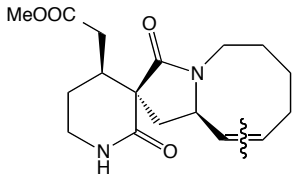
The successful applicability of olefin metathesis to so many different fields of science and the incredible revolution that this reaction brought to modern organic chemistry were recognized in 2005 by the Royal Swedish Academy of Sciences that conferred the Nobel prize in chemistry to Yves Chauvin, Richard Schrock and Robert Grubbs.[54]

1.5 Ring-closing metathesis (RCM): application in organic synthesis.

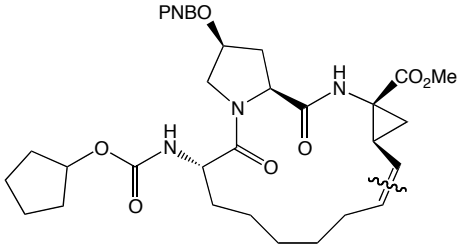
As much as ROMP and ADMET had, in the last 15 years, a great impact on polymer chemistry, RCM imposed itself as the most flexible, easily applicable and atom economic method to generate unsaturated small, medium, and large rings in organic synthesis.[55]



(+)-Elatol



ADE-Ring System of Nakadomarin A



HCV Protease Inibitor BILN 2061

Figure 24. Some examples of successful applications of RCM in the synthesis of complex natural products featuring ring of different size.[56]

This innovation revolutionized in particular the field of complex natural products synthesis.[57] Some examples of the significance of RCM in this field are shown in Figure 24.

Olefin metathesis, as shown by the mechanism proposed by Chauvin, is a process that is normally fully reversible. This implies that a driving force must to be present in order to obtain a single, defined product. For example, in ROM and ROMP the reaction is driven by the release of the ring strain. For RCM and CM the equilibrium is usually driven in the desired direction by progressive removal of one of the products from the reaction environment (generally ethene or propene, liberated as gas). Examples of RCM reactions in which non-volatile products are produced (styrene for example) are known and, for specific applications, important results have been obtained.

As previously observed in Figure 2 a classical problem in RCM reactions is connected with the presence of a competitive reaction: ADMET. A plethora of factors has to be taken into account in order to understand which one of the two processes will be dominant:

1) Small (5 and 6 atoms) and large (more than 15 atoms) rings normally can be easily obtained via RCM. For medium sized cycles (8-14 atoms) ring strain is a problem and often ADMET is dominant.
2) Presence of substitutents that induce a strong Thorpe - Ingold effect favors RCM products.[58]
3) Presence of one terminal electron poor olefin favors ADMET processes. α,β-unsaturated ester are particularly problematic, as they also reduce the conformational freedom of the molecules favoring a linear arrangement in space.
4) In the presence of an heteroatom that may chelate the metal, RCM is generally favored but the reaction rate is slower and higher temperature could be necessary.[59]
5) High dilutions favors RCM but have a remarkably negative effect on the catalyst performance.[60]

The concentration effect is one of the easier factors to manipulate ond has been widely studied, as demonstrated by the numerous reports that describe the importance of high dilution for the synthesis of macrocycles.[61] Surprisingly almost no attempts of

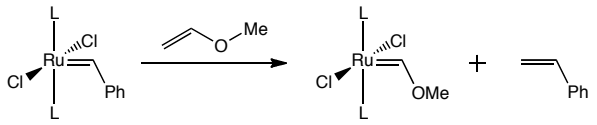
testing the effect of high concentration on RCM reactions that generate medium and small rings have been reported in literature.[62] One of the main focuses of this thesis has been directed to this topic and the results will be presented in Chapter 2.

1.6 Ring-closing metathesis of heteroatom-substituted olefins

The discovery of well defined, ruthenium-based metathesis catalysts, featuring greatly increased functional group tolerance, allowed, in the last ten years, a broadening of the scope of the olefin metathesis reaction. Nevertheless, some important limitations are still present, principally connected to substrates featuring directly functionalized olefins. Strongly electron-donating or electron-withdrawing groups are indeed able to drastically modify the reactivity of a double bond towards the metal.

Electron rich olefins

When the olefin substituent increases the electron density of the double bond, a fast reaction with the catalyst generates a Fisher-type carbene (**21**), too stable to further react in the catalytic cycle (Figure 25). This reaction is normally so fast, quantitative and irreversible that vinyl ethers have become common reagents for quenching metathesis catalysts.



21

Figure 25. Reaction between a general metathesis catalyst and an electron rich olefin.

By employing harsh conditions and using the more stable ruthenium-based catalysts now available, some groups succeeded in performing successful RCM of enol ethers and enamines. In general, substrate scope is however very limited, catalyst loading must be high, and only few turnovers can be achieved.[63]

Electron poor olefins

When electron poor olefins are used, electron-deficient, poorly stable metal carbene species are formed. Moreover, the low propensity of these olefins to coordinate and react with the catalyst represents a major problem. In these cases chelation of an heteroatom of the substrate to the metal center often becomes competitive with coordination of the olefin and a drastic reduction of the reaction rate is observed. This behavior is particularly well documented in literature for α,β-unsaturated carbonyl compounds (Figure 26).[64]

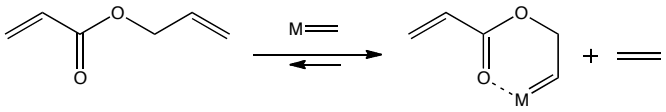


Figure 26. Possible deactivation of the catalyst via intramolecular heteroatom chelation.

Various attempts to solve this problem were performed, and the use of a stoichiometric amount of Lewis-acid (usually bulky Ti-based molecules) that can pre-chelate the carbonyl function proved to be quite successful.[65]

Vinyl halides constitute another class of electron poor olefins of great synthetic interest that proved to be challenging substrates for RCM reactions. Pioneering work in this field was reported by Weinreb with vinyl chlorides. Even though a high catalyst loading was required (10% **GII**), Weinreb was able for the first time to generate a series of 5-, 6- and 7-membered vinyl chlorides in good overall yields.[66]

Later on, Brown,[67] Rutjes[68] and Haufe[69] demonstrated that substrate containing vinyl fluorides and trifluoromethyl-substituted olefins undergo RCM (Figure 27). However, the drastic reaction conditions employed represented a serious limit, often inducing partial decomposition of the starting material.

Vinyl bromide substrates proved to be, to date, completely inactive with both Schrock-type and first or second-generation Grubbs-type catalysts.[70] In Chapter 4 of this thesis a first, partial solution to these problems will be presented, demonstrating

how appropriate modifications of the starting vinyl halide can lead to efficient RCM of these substrates with a catalytic amount of a commercially available catalyst.

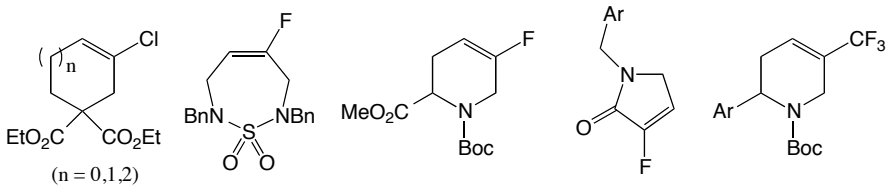
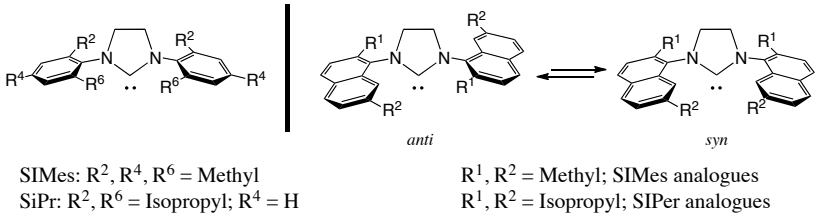


Figure 27. Some successful examples of products formed via RCM reaction of vinyl halides.

Other electron poor olefins, substituted with sulfur or phosphorus atoms, have been used as RCM substrates with good results generating 5, 6 and 7 membered heterocycles.[71] Particularly fascinating in this area is the work of Hoveyda, who by using enantiomerically enriched molybdenum based catalyst, was able to generate in average to good yields enantioenriched cyclic phosphinates and phosphine oxides.[72]

1.7 Olefin metathesis in Dorta's laboratory

Early work developed in our laboratories has led to the synthesis of promising members of a new family of stable, saturated free NHC ligands that incorporate bulky naphthyl side chains. The introduction of the naphthyl moieties generates atropoisomeric ligands with C_2-symmetric (*anti*) and C_s-symmetric (*syn*) conformations (Figure 28).



SIMes: R^2, R^4, R^6 = Methyl
SiPr: R^2, R^6 = Isopropyl; R^4 = H

R^1, R^2 = Methyl; SIMes analogues
R^1, R^2 = Isopropyl; SIPer analogues

Figure 28. Imidazolin-2-ylidenes with phenyl (left) and naphthyl (right) side chains.

The first applications of these types of ligands in Grubbs second-generation ruthenium type complexes proved to be quite successful, and some of the new catalysts appeared to be superior to the original SIMes-containing Grubbs second-generation complex in simple RCM reactions leading to di-substituted olefins.[73]

Already at this early stage the idea of separating the isomers to test their reactivity and stability was developed but, despite numerous attempts, the process was always unsuccessful, mainly due to fast decomposition of the catalysts.

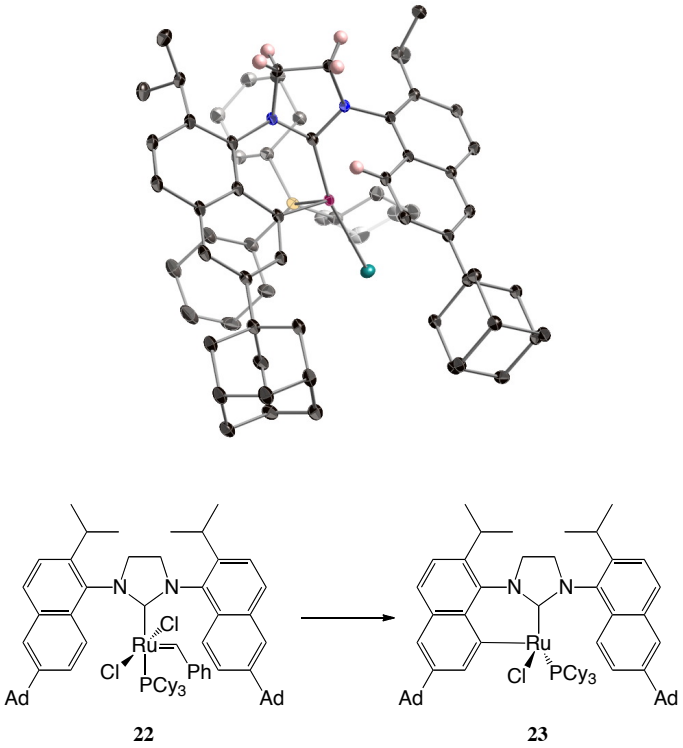


Figure 29. Ellipsoid view (30% probability) and ^{1}H NMR spectrum of decomposition product **22**.

The work was then extended and a screening of the substituents on the naphthyl side chains was performed.[74] Bulky, cyclic or linear substituents in position 2 of the ring were fundamental for the activity of the catalyst; substituents in position 2 and 7 improved the overall catalytic performance, particularly when substrates generating tri- and tetra-substituted olefins were used. Finally and in some way surprisingly,

simply switching from a 2,7- to a 2,6-substitution on the naphthyl ring, a clear drop in catalytic performance was observed.

A crystal structure obtained from the decomposition of one of these catalysts (**22**, Figure 29) helped to rationalize this trend: in the absence of a substituent in position 7 of the naphthyl ring, the ligand can undergo intramolecular cyclometalation, generating an inactive species.

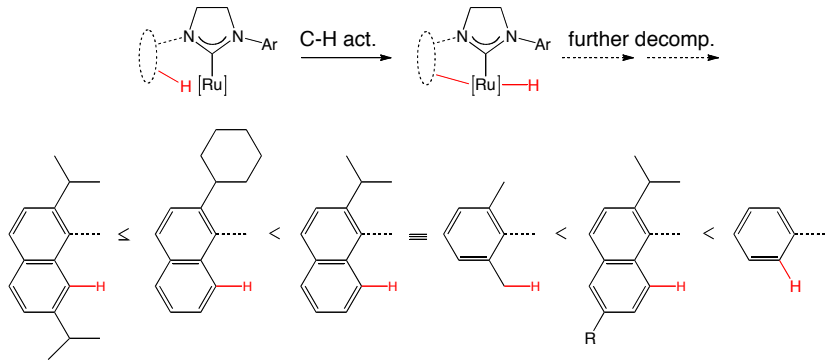


Figure 30. Plausible order of C-H activity for different side chains.

The presence of substituent in position 7 clearly disfavors this decomposition pathway for steric reasons. Substituents in position 6 instead probably increase the electron-density in position 8 and enhance the likelihood of a C–H activation; this leads to the least active catalyst (Figure 30).

Mimics of the second-generation Hoveyda-type catalyst were also developed and tested and the reactivity of this new family of catalysts proved to be similar, or, in the best cases, slightly superior with respect to the original catalytic system.[75] Again, separation of the two diasteroisomers was attempted but no significant results were obtained.

1.8 Aim of the thesis (Summary)

As already mentioned, in the last twenty years olefin metathesis has become one of the more important tools to manipulate carbon-carbon double bond. Despite the great advancement obtained in catalyst stability, activity and functional group tolerance, further improvement are still highly desirable. Following this lead, the

work described in this thesis is dedicated to the synthesis of novel catalysts and to the study of their behavior in ring-closing metathesis (RCM) reactions.

The first part of the work, described in Chapter 2, focuses on the development of a series of new ruthenium-based metathesis catalysts of the Hoveyda-Blechert family incorporating *N*-heterocyclic carbenes featuring substituted naphthyl side chains. Chromatographic separation and purification of the *syn* and *anti* isomers of some of these catalysts was, for the first time, possible. Through a series of kinetic studies performed on the isolated isomers, a remarkable difference in activity/stability between the *anti* and the *syn* conformers of the catalyst was observed.

Extensive studies on the effect of the concentration on the reaction rate of RCM reactions have also been performed, proving that, under particular conditions, very high concentration of the starting diene can lead to RCM of a variety of substrates with extremely low catalyst loading.

In Chapter 3 the synthesis and characterization of a new family of NHC featuring mono- or di-substituted naphthyl side chains is presented. The goal of this work was to obtain ligands able to adopt predominantly the *anti* conformation. This will allow for a wider use of these compounds in organometallic chemistry and as organocatalysts in general, and for incorporation of the ligands in Ru-catalysts for olefin metathesis reactions in particular.[76]

Finally in Chapter 4, the development of a catalytic method to access cyclic alkenyl bromides via the RCM reaction using a catalytic amount of a commercially available catalyst will be presented. These products are of great interest as building blocks in organic synthesis and new, mild synthetic pathways to access them are highly desirable. Preliminary attempts to clarify the mechanism of the reaction will be presented.

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CHAPTER TWO

Impact of NHC Ligand Conformation and Solvent Concentration on the Ruthenium-Catalyzed Ring-Closing Metathesis Reaction

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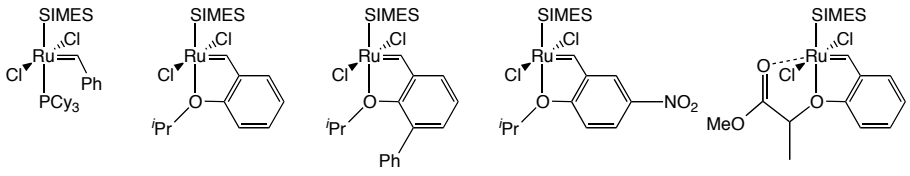
(*J. Am. Chem. Soc.* **2009**, *131*, 9498)

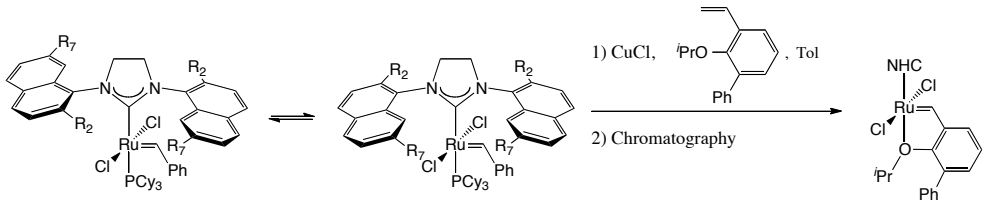
Ring-closing metathesis (RCM) reactions promoted by transition metal catalysts have gained enormous importance in synthetic organic chemistry.[1] Especially valuable was the introduction of ruthenium-based N-heterocyclic carbene complexes such as Grubbs' II (**GII**) a decade ago.[1] Since then, major research efforts have been directed toward optimizing the ligand sphere around the ruthenium center and have led, inter alia, to derivatives shown in Figure 2.1.[2] Overall though, activities of these catalysts in RCM, while sufficient for laboratory-scale applications, are still relatively low for applications in larger-scale reactions.



Our entry into this fascinating field of research began via the identification of saturated NHCs that feature substituted naphthyl side chains.[3] The ligands are present as a mixture of *anti* and *syn* conformers, and preliminary data with two of these NHCs, (2,7)- SIPrNap and (2)-SICyNap, outlined their high catalytic activity in the RCM of **GII** type precatalysts (used as isomeric mixtures).[3c] The substitution pattern

on the naphthyl side chains confers a high degree of conformational stability,[3a,4] and we were therefore intrigued by the prospect of metathesis-active NHC-ruthenium complexes that are only distinguished by the relative orientation of their side chains.[5]

Scheme 1. Preparation and Separation of Catalysts **3** and **4**



R^2, R^7 = ^{i}Pr; (2,7)-SiPrNapRuCl$_2$(=CHPh)(PCy)$_3$ **1** (1:1)

R^2=Cy R^7=H; (2)-SiCyNapRuCl$_2$(=CHPh)(PCy)$_3$ **2** (4:1)

{ *anti*-**3** (42 % yield)
{ *syn*-**3** (21 % yield)
anti-**4** (62 % yield)

To enhance the possibility of separating such complexes and at the same time ensure high catalytic activity, we decided to prepare phosphine-free ruthenium precatalysts that are analogues to Blechert's catalyst (**BleII**).[2b] Complex **3** was prepared from an *anti*/*syn* mixture (ca. 1:1) of **1** by metathesis with *o*-isopropoxy-*m*-phenylstyrene (Scheme 1). Careful chromatographic workup of the isomeric mixture led to the isolation of the two complexes *anti*-**3** (first compound eluted) and *syn*-**3** in 63% overall yield. When the same reaction was performed with an *anti*/*syn* (4:1) mixture of **2**, only the first isomer, namely *anti*-**4**, was isolated from the column (62% yield).[6] The assignment of the respective isomers was verified through X-ray structural studies of complexes *anti*-**3** and *anti*-**4** (Figure 2.3).

RCM activities (27 °C, 0.1 M substrate/CD_2Cl_2) of complexes *anti*-**3**, *syn*-**3**, and *anti*-**4** were then benchmarked against Blechert's SIMes-derived catalyst (**BleII**) using a series of substrates (**5**-**15**, Figure 2.4) and following their conversion by 1H NMR spectroscopy. Selected kinetic data are shown in Figure 2.4 (see the Supporting Information for more details). As anticipated based on our earlier studies on **GII** derivatives, the modification of the NHC structure has a beneficial effect on the reactivity profile and the following overall order of activity can be deduced: *anti*-**3** > *anti*-**4** > *syn*-**3** > **BleII**.

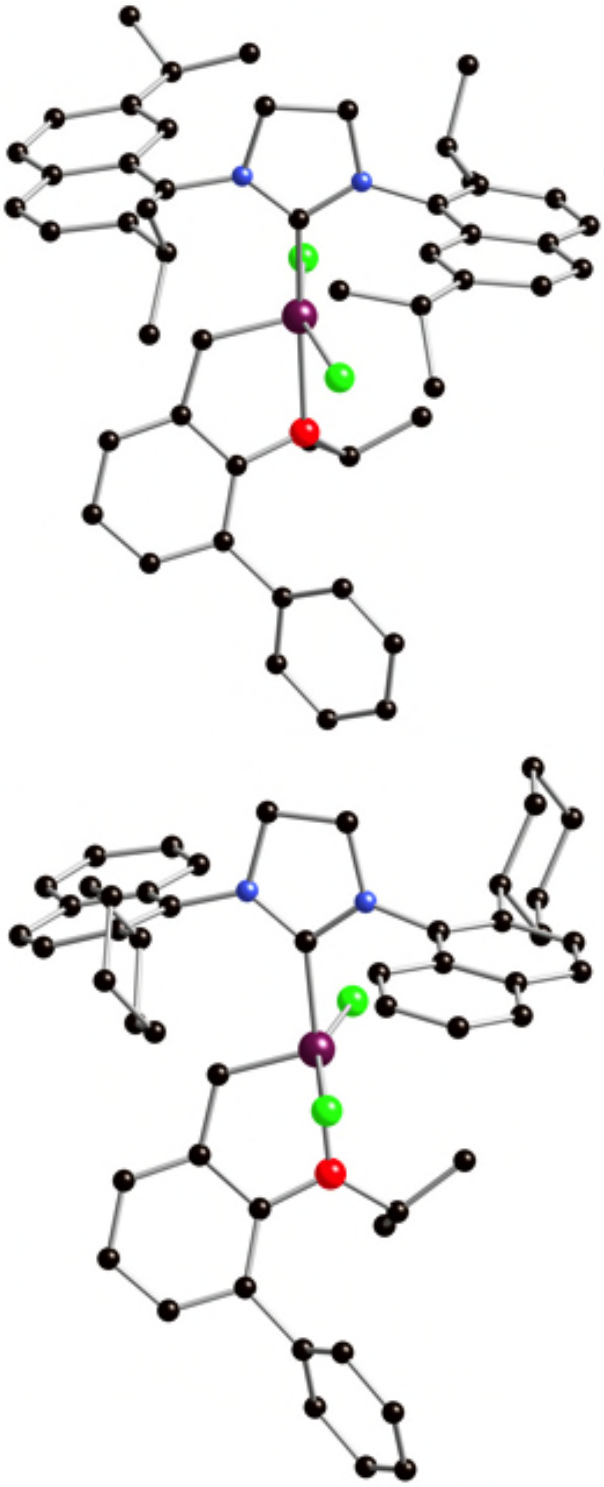


Figure 1. Ball-and-stick drawing of *anti*-**3** (left) and *anti*-**4** (right)

Somewhat surprising is the fact that differences in activity favoring (2,7)-SIPrNap and (2)-SICyNap over SIMes increase with bulkier substrates that give tri- and tetrasubstituted cyclic olefins or with dienes that produce six-membered cycloolefins.[7] Here, both *anti*-**3** and *anti*-**4** clearly outperform *syn*-**3** and in particular **BleII**, and the overall reactivity profile puts them among the most active RCM catalysts known.

While the higher reactivity of the new catalysts as well as the clear differences between *anti*-**3** and *syn*-**3** looked very interesting, we were puzzled by the fact that the **BleII** catalyst seemed to perform better than originally reported by Blechert et al.[2b] A closer inspection of their report shows that the reaction conditions used, except for substrate concentration (and catalyst loading), were identical. This prompted us to examine the dependence of reaction concentration on RCM activity. To do so, we chose the overall most active precatalyst (*anti*-**3**, 0.1 mol %) and moderately bulky substrate **7**. Figure 2.4 (below right) shows that reaction rates indeed increase dramatically with increasing substrate-to-solvent concentrations. Using Blechert's dilution (0.01 M substrate/CD_2Cl_2) or a 0.04 M concentration does not lead to full conversion of **7**, while a high concentration (0.8 M) ensured complete conversion after only 21 min. More significantly, a reaction run in an open vessel without any solvent gave quantitative yields of the product within 2 min, without generating any byproducts that arise from ADMET.[8,9]

As a result, neat reactions with other substrates at lower catalyst loadings were performed with *anti*-**3** (Table 1). In some cases, namely for the tosylamide-derived substrates, the products were solids at room temperature and impeded simple, neat reaction runs. Here, a concentrated hexane solution of *anti*-**3** was added to the neat substrates giving pure solid products with almost the same efficiency as that of the neat reactions.

Overall, catalyst loadings could be significantly lowered compared to the runs performed in solution. Although not optimized, between 50 and 250 ppm of precatalyst *anti*-**3** at room temperature suffice for virtually complete conversion to give ring-closed disubstituted and trisubstituted five- and six-membered rings. Generation of ethylene gas is not necessary for the reaction to proceed (entries 13-15).

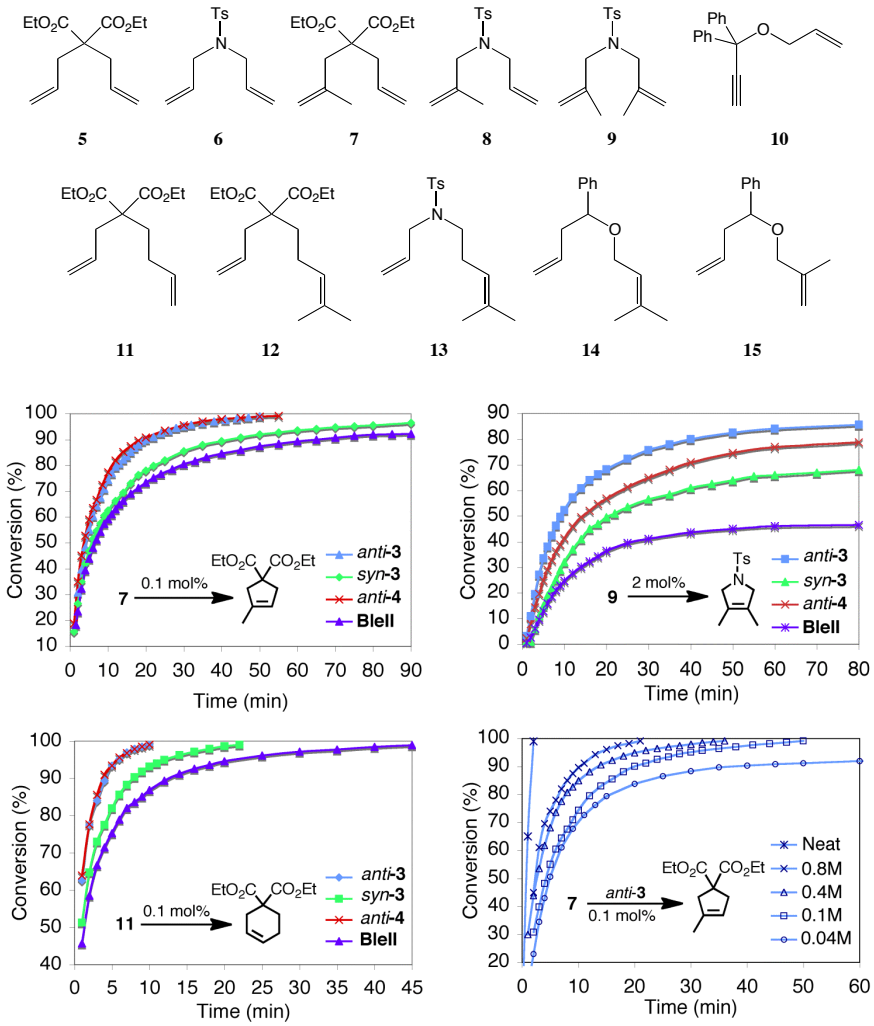


Figure 2. Substrates (above, catalyst loadings for **5**-**8**, **10**-**14**: 0.1 mol %; For **15**: 0.2 mol %; For **9**: 2 mol %), kinetic data for RCM of **7**, **9**, and **11**, and concentration dependence for conversion of **7** with *anti*-**3** (below).

In the case of the representative enyne substrate **10**, a concentrated CH_2Cl_2 solution already ensures unprecedented levels of activity (entries 9,10). Also notable is the very low catalyst loading (0.2 mol %) needed to obtain the tetrasubstituted olefin from **9** (entry 8). This product is normally only produced with heating and substantially higher catalyst loadings. Turnover numbers reaching 20,000 (entries 2,10,12) and turnover frequencies of 240,000 per hour (entries 1,11,13) for complete conversion certainly approach values needed for larger-scale industrial applications of

the RCM reaction.[10]

Table 1. RCM (25°C) with anti-3 at low catalysts loadings

entry	olefin	conditions	*anti*-**3** (ppm)	*t* (min)	yield (%)[a]
1	**5**	neat	250	1	99 (97)
2[b]	**5**	neat	50	120	97
3[c]	**6**	0.5 M Hex	250	5	98 (96)
4[c]	**6**	0.5 M Hex	100	12	97
5	**7**	neat	250	30	98 (97)
6[c]	**8**	0.5 M Hex	250	9	99
7[c]	**8**	0.5 M Hex	100	18	97
8[c]	**9**	0.5 M Hex	2000	480	97
9[c]	**10**	0.5 M DCM	100	4	99
10[c]	**10**	0.5 M DCM	50	30	99
11	**11**	neat	250	1	99
12[b]	**11**	neat	50	120	98
13	**12**	neat	250	1	99
14[c]	**13**	0.5 M Hex	250	5	99
15	**14**	neat	250	480	96
16	**15**	neat	250	480	97

[a] Yields based on NMR analysis. Selected isolated yields in brackets. [b] Runs with **GII** did not go to completion under these conditions but showed appreciable amounts of product [after 2 h: 72% (**5**) and 58% (**11**), after 24 h: 87% (**5**) and 72% (**11**)](ref 6). [c] DCM = CH_2Cl_2, Hex = *n*-hexane.

In conclusion, we have identified ruthenium metathesis catalysts that show improved reactivity profiles for the RCM and where clear differences exist between the respective conformers of the NHC ligand. While testing these new catalysts, we discovered that substantially higher reaction rates could be obtained when more concentrated substrate/solvent mixtures were employed. This ultimately led to the RCM forming five- and six-membered rings of a variety of substrates with catalyst loadings of just 50-250 ppm of *anti*-**3**. This simple and practical way for improving the reactivity and the lifetime of *anti*-**3** seems to be applicable to other ruthenium metathesis catalysts and should extend their usefulness in chemical synthesis. The intriguing reactivity differences between *anti*-**3** and *syn*-**3** are now the subject of a mechanistic study that will be extended to metathesis reactions using chiral derivatives of the ligands described here.[11]

Acknowledgment. We thank the Alfred Werner Foundation (R.D.), the Swiss National Foundation (R.M.), the Roche Research Foundation (E.D.), and UZH (M.G., L.V.P., X.L.) for support.

2.1 Supplementary Data

In the attempt to improve the results obtained with catalyst **3** and **4** we decided to synthesize and test a family of catalysts featuring different substituents in position 2 of the naphthyl side chains (Figure 3).

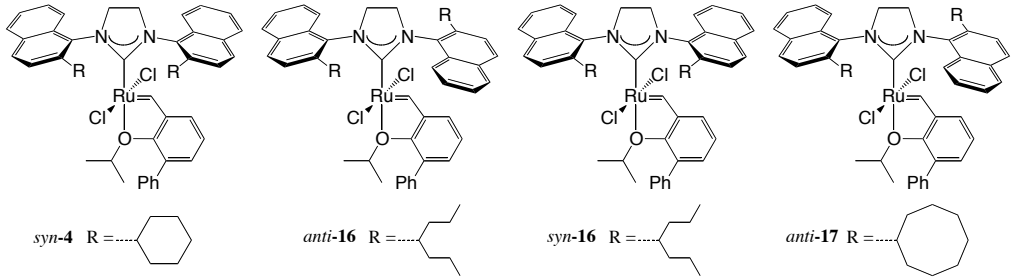


Figure 3. Second-generation Hoveyda-Blechert type catalysts.

All the desired compounds were obtained in moderate to good yields using a new one-pot procedure starting from the corresponding free carbenes and **GI**. The in situ generated **GII**-type catalyst was, without any purification, directly reacted with an excess of the desired modified styrene and with CuCl to furnish the crude desired **BleII**-type analogues (see supporting information for details). The previously developed purification procedure was also improved and this led to a higher purity of the final compound and to a much easier separation of the isomers (*anti*-**16** and *syn*-**16** were obtained in good yield in an almost 1:1 ratio). Moreover, the isolation of compound *syn*-**4**, previously observed in the crude reaction mixture but never isolated due to its instability during the work up procedure, was now possible.

The assignment of the conformation of compound *anti*-**16** was verified through X-ray structure study and the thermal ellipsoid drawings are reported in Figure 4.

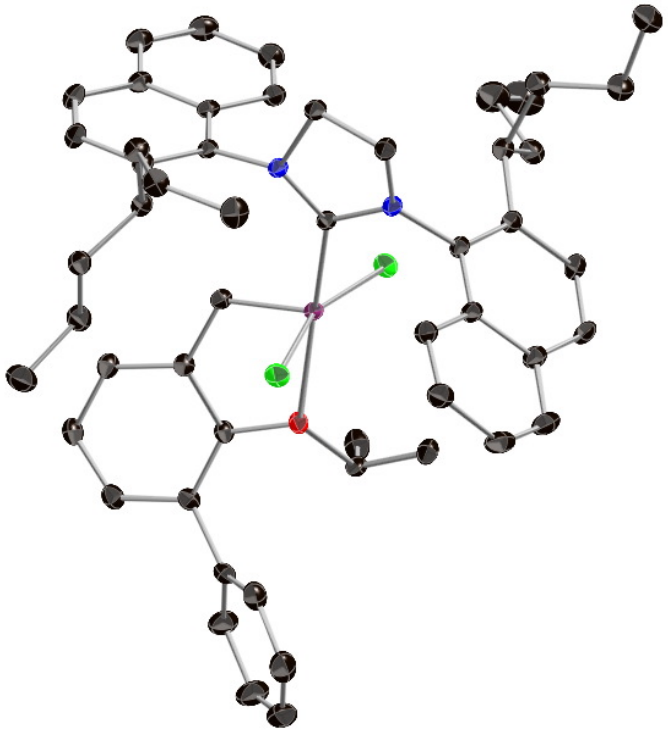


Figure 4. Thermal ellipsoid drawing (30 % probability) of *anti*-**17**. Hydrogen atoms were omitted for clarity.

As a first test we decided to compare the *anti* and the *syn* isomers of catalysts **4** and **16** to understand if, as previously observed with catalyst **3**, the *syn* form was indeed less active/stable than the *anti* configured NHC-containing catalysts in RCM. Substrates **7** and **8** were chosen for the kinetic studies, as they are known to be challenging substrates for RCM reaction at low catalyst loading and at room temperature. This ensured longer reaction time and, as a consequence, meaningful kinetic curves.

The obtained results are reported in Figure 5 and clearly confirmed the trend previously observed. Moreover the analysis of the kinetic data collected showed that there was only a small difference between the reactivity of catalyst **4**, that features rigid cyclic substitutions on the naphthyl side chains, and **16**, that feature flexible linear alkyl chains (both for the *syn* and *anti* isomers, Figure 5).

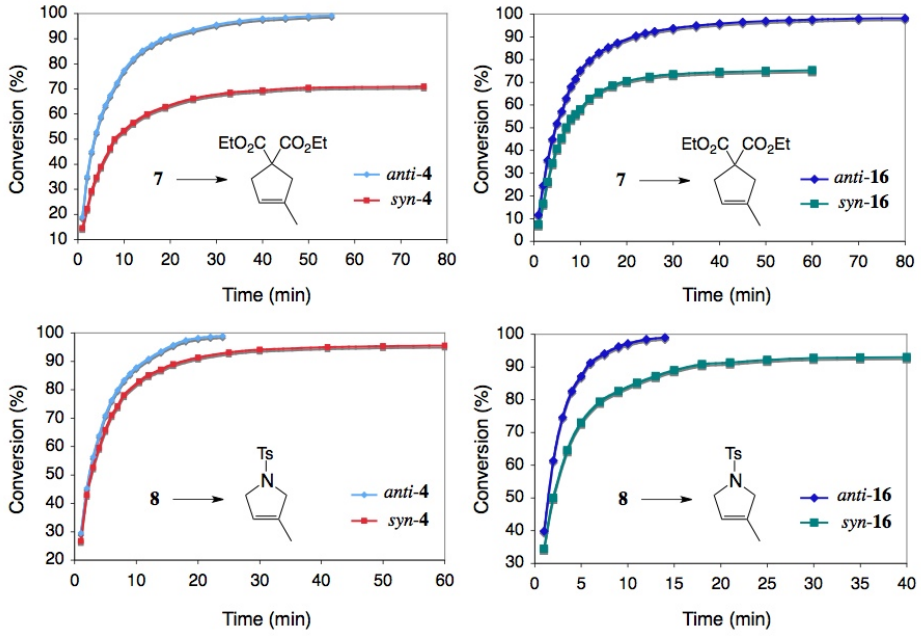


Figure 5. Kinetic studies of *syn* and *anti* isomers of catalyst **4** and **17** in RCM reaction of substrates **7** and **8**.

A quite significant difference was instead observed when the catalytic performances of the *syn* isomers of catalysts **4** and **17** were confronted with the results obtained with *syn*-**3** (Figure 6).

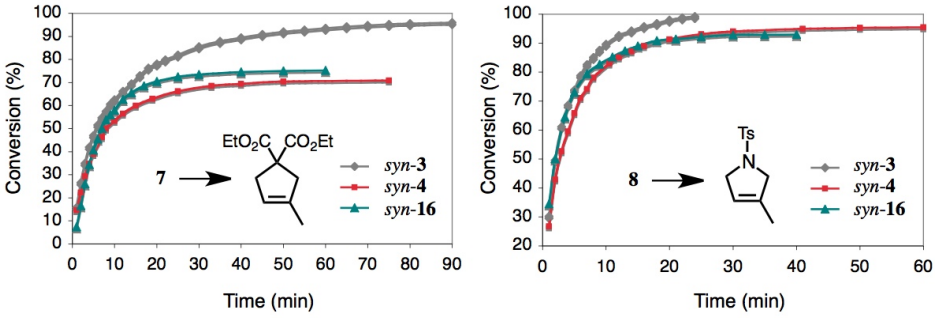


Figure 6. Confront of the catalytic performance of the *syn* isomers of catalysts **3**, **4** and **17**.

All the catalysts presented a similar fast activation period but, in a second phase of the reaction, catalyst *syn*-**3** proved to be more stable and able to perform RCM for a

longer overall period of time. It is possible to speculate that the higher stability observed with catalyst **3** could be connected with the presence of a substituent in position 7 of the naphthyl side chains[12] but to verify this hypothesis more through kinetic studies with catalysts incorporating a wide range of naphthyl-based NHC ligands must be performed.

In the attempt to create a catalyst displaying at the same time high activity and good stability we decided to substitute one of the two naphthyl side chains with a bulky di-substituted aryl moiety. The obtained compound was no more present in solution as a mixture of diastereoisomers (*syn* and *anti*) but as a racemic mixture of enantiomers (Figure 7).

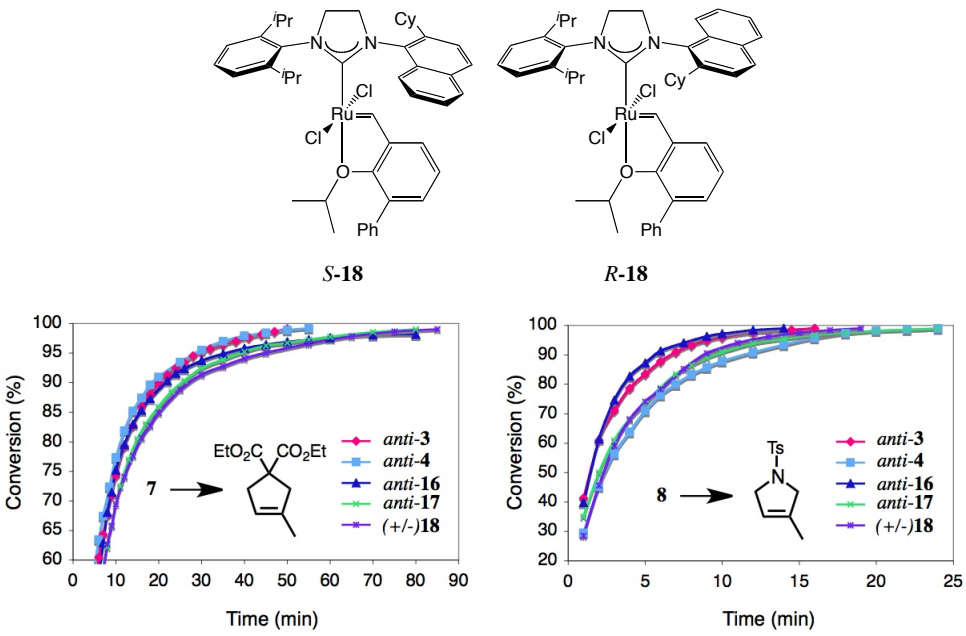


Figure 7. Structure of compound **18** (above); comparison of the catalytic performance of the *anti* isomers of catalysts **3**, **4**, **16**, **17**, and **18** (below).

To evaluate the catalytic activity of **18** we collected kinetic data using again substrates **7** and **8**. In figure 7 are reported the obtained results, compared with the one recorded using the other catalysts. We were pleased to observe that indeed catalysts **18** present good activity. These observations, together with the easier synthesis and purification, make **18** and its congeners featuring similar NHC design an appealing

candidate for future catalyst development and for future applications in organic synthesis.

2.2 Experimental Section

General procedures. All reactions were carried out using standard Schlenk or glovebox (Mecaplex or Innovative Technology) techniques under nitrogen. All reagents were used as received unless otherwise noted. Solvents were purchased in the best quality available, degassed by purging thoroughly with nitrogen and dried over molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Solvents for NMR spectroscopy were degassed with nitrogen and dried over molecular sieves. NMR spectra were collected on AV2 400 or AV2 500 MHz Bruker spectrometers. Chemical shifts are given in ppm. The spectra were calibrated to the residual ^{1}H and ^{13}C of the solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). High-resolution electrospray ionization mass spectrometry was performed on a *FinniganMAT 900* (Finnigan MAT95, San Jose, CA; USA) double-focusing magnetic sector mass spectrometer (geometry BE). GC- MS analysis was done on a Finnigan Voyager GC8000 Top. Elemental analysis was done on a Leco CHN-932 analyzer. X-ray crystallography was performed on a Nonius KappaCCDarea-detector diffractometer using graphite-monochromated Mo K radiation (= 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Compounds **6**,[13] **7**,[14] **8**,[15] **9**,[16] **10**,[17] **11**,[18] **12**,[19] **13**,[20] **14**,[21] and **15**,[22] were prepared according to literature procedures.

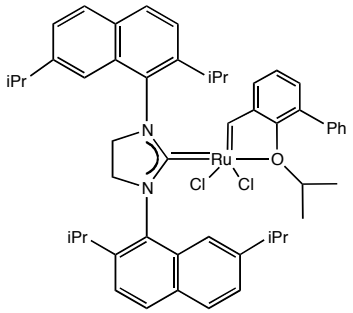
Synthesis of the catalyst

Synthesis of catalyst **3**

In a glovebox, a ca. 1:1 *anti/syn* mixture of complex **1** (0.100 g, 0.097 mmol) and CuCl (0.011 g, 0.110 mmol) were placed in a Schlenk tube and methylene chloride (4

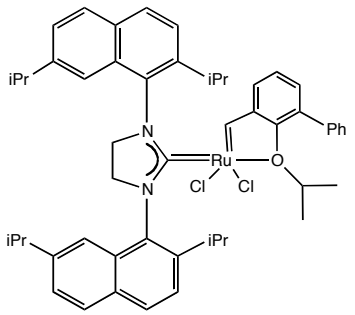
ml) was added. Styrene **e** (0.046 g, 0.180 mmol), dissolved in methylene chloride (4.0 ml), was then added and the resulting bright violet solution was stirred at 45°C for 90 min. During this time the color moves to brown and, when the reaction is completed, to dark green. The solvent was evaporated and the crude catalyst was purified by column chromatography (Hexane – CH_2Cl_2 6:4 to 1:1) to afford the two conformers *anti*-**3** (0.042 g, 0.048 mmol) and *syn*-**3** (0.021 g, 0.024 mmol) in 63% overall yield.

Data for *anti*-**3** are as follows:



^{1}H NMR (CD_2Cl_2, 400 MHz): δ 16.3 (s, 1H), 8.2 (br, 4H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.27 (m, 6H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.65 (dd, *J* = 7.55 – 1.5 Hz, 1H), 4.44 (s, 4H), 4.22 (sept, *J* = 6.3 Hz, 1H), 4.15 (br, 2H), 3.13 (sept, *J* = 7.0 Hz, 2H), 1.4 (m, 24H), 0.67 (d, J= 6.2 Hz, 3H), 0.62 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR (CD_2Cl_2, 100 MHz): δ 294.2, 213.4, 149.5, 148.1, 146.8 (br), 139.7, 133.3, 132.3, 131.8, 130.1, 129.8, 128.9, 128.1, 127.9, 126.8 (br), 123.8, 123.7, 122.4 (br), 121.5, 77.8, 34.9, 32.1, 29.5, 26.2, 24.0, 23.6, 23.2, 23.1, 20.59, 20.6, 14.4. MS (ESI) calculated for $C_{51}H_{58}N_2O_1Cl_2Ru_1$: 887.0. Found 851.5 $[M\text{-}Cl]^+$. HRMS (ESI) calculated for $^{12}C_{51}H_{58}{}^{14}N_2O_1{}^{35}Cl_2{}^{104}Ru$: 888.9950. Found 818.3850 $[M\text{-}2Cl]^+$. Elemental analysis calculated for $C_{51}H_{58}N_2O_1Cl_2Ru_1$: C 69.06, H 6.59, N 3.16; found C 69.37, H 6.74, N 2.89.

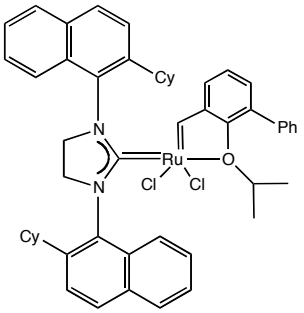
Data for *syn*-**3** are as follows:



^{1}H NMR (CD_2Cl_2, 400 MHz): δ 16.3 (s, 1H), 8.2 (br, 4H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.27 (m, 6H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.65 (dd, *J* = 7.55 – 1.5 Hz, 1H), 4.44 (s, 4H), 4.22 (sept, *J* = 6.3 Hz, 2H), 4.15 (br, 1H), 3.13 (sept, *J* = 7.0 Hz, 2H), 1.4 (m, 24H), 0.67 (d, J= 6.2 Hz, 3H), 0.62 (d, J= 6.2 Hz, 2H). ^{13}C NMR (CD_2Cl_2, 400 MHz): 295.1, 213.6, 149.6, 148.0, 147.4, 146.7 (br), 139.8, 133.4, 132.4, 131.8, 129.8, 129.4, 128.9, 128.1, 125.9 (br), 123.9, 123.7, 123.5 (br), 121.5, 77.9, 35.3, 30.3, 29.6, 26.1, 24.5, 23.9, 22.9, 22.3, 20.3, 12.3. MS (ESI) calculated for $C_{51}H_{58}N_2O_1Cl_2Ru_1$: 887.0. Found 851.5 $[M\text{-}Cl]^+$. HRMS (ESI) found 851.3272 $[M\text{-}Cl]^+$. Elemental analysis calculated for $C_{51}H_{58}N_2O_1Cl_2Ru_1$: C 69.06, H 6.59, N 3.16; found C 69.00, H 6.69, N 3.11.

Synthesis of catalyst **4**

In a glovebox, a ca. 4:1 *anti/syn* mixture of complex **2** (100 mg, 0.099 mmol) and CuCl (30 mg, 0.300 mmol) were placed in a Schlenk tube and methylene chloride (5 ml) was added. Styrene **e** (51 mg, 0.200 mmol) in methylene chloride (5.0 ml) was then added and the resulting bright violet solution was stirred at 45° C for 30 min. During this time the color changes to brown and, when the reaction is completed, to dark green. The solvent was evaporated and the crude catalyst was purified by column chromatography (Hexane – CH_2Cl_2 6:4 to 1:1) to afford the desired product *anti*-**4** (54 mg, 0.061 mmol) in 62%.



^{1}H NMR (CD_2Cl_2, 400 MHz): δ 16.22 (s, 1H), 8.43 (br, 2H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.65 (m, 4H), 7.50 (t, *J* = 7.1 Hz, 2H), 7.24 (m, 5H), 7.14 (dd, *J* = 5.52 – 1.6 Hz, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 6.38 (dd, *J* = 7.6 – 1.6 Hz, 1H), 4.44 (m, 4H), 4.2 (sept, *J* = 6.2 Hz, 1H), 6.34 (m, 2H), 2.0 – 1.2 (m, 20H), 0.62 (d, *J* = 6.2 Hz, 3H), 0.58 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 295.7, 214.8, 149.3, 147.3, 145.3, 139.7, 133.2, 133.1, 131.9, 131.2, 131.1, 129.6, 129.3, 128.4, 127.9, 127.6, 127.3, 126.2, 125.5, 123.1, 121.6, 54.7, 40.0, 32.7, 27.8, 26.9, 26.8, 20.5, 20.4. MS (ESI) calculated for $C_{51}H_{54}N_2O_1Cl_2Ru_1$: 882.3. Found 846.8 $[M\text{-}Cl]^+$. HRMS (ESI) calculated for $^{12}C_{51}H_{54}{}^{14}N_2O_1{}^{35}Cl_2{}^{96}Ru_1$: 841.30007. Found 841.30004 $[M\text{-}Cl]^+$. Elemental analysis calculated for $C_{51}H_{54}N_2O_1Cl_2Ru_1$: C 69.37, H 6.16, N 3.17; found C 69.01, H 6.27, N 3.16.

Comments and spectra of crude mixtures of 3 and 4

Column chromatography of **3** and **4** leads to some degradation of the complexes. This is the reason why the *syn*-isomer of complex **4** could not be recovered and the initial *anti*/*syn* mixture of **3** is not maintained (1:1 going to 2:1). 1H NMR spectra of crude mixtures of **3** and **4** before column chromatography are shown below to illustrate this point.

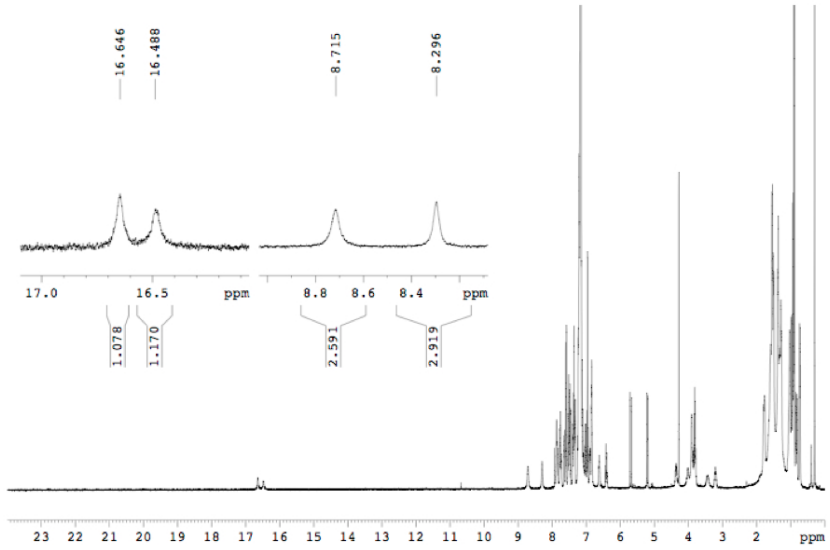


Figure S1. ^{1}H NMR spectrum (C_6D_6, 10°C) of a crude mixture of anti/syn-3. Zoomed-in regions show benzylidene signals and H^8-protons of the naphthyl side chains.

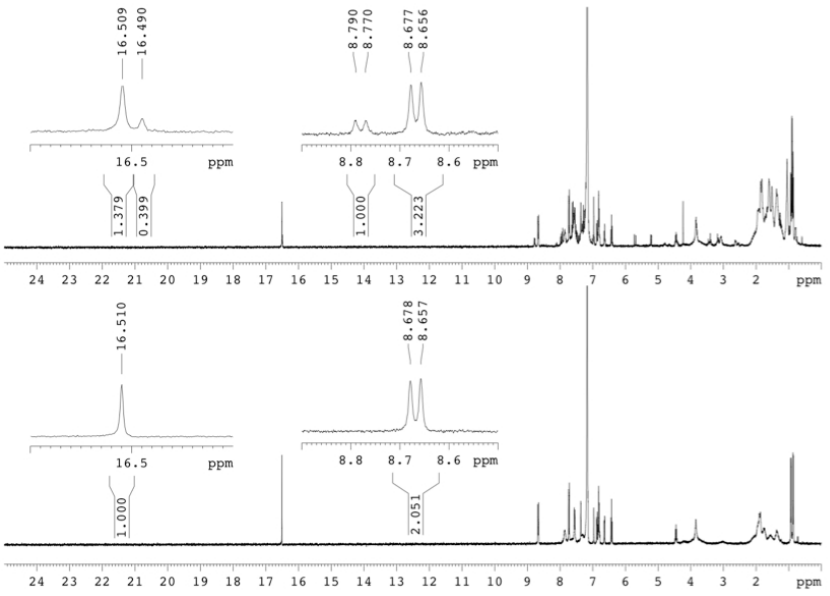
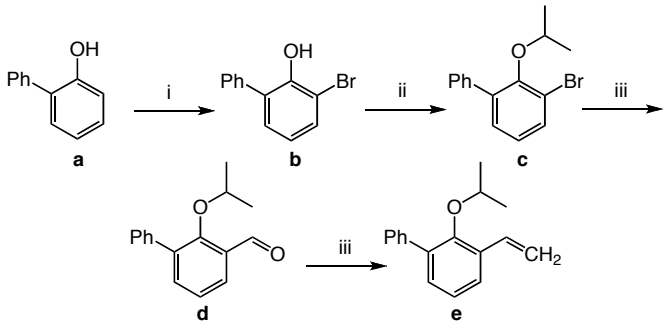


Figure S2. ^{1}H NMR spectra (C_6D_6, 10°C) of a crude mixture of *anti*/*syn*-4 (above, before column chromatography) and of *anti*-4 (below, after column chromatography).

Zoomed-in regions show benzylidene signals and H^8-protons of the naphthyl side chains.

Synthesis of the styrene precursor

The synthesis of **e** follows a combination of standard synthetic procedures. However, the synthetic pathway to **e** shown below is more scalable than other procedures insofar as it does not need any chromatographic workup.



Scheme S1. Procedure for the synthesis of the styrene derivative

2-Bromo-6-phenylphenol (b): The procedure reported from Mu[23] was used with some modification. Br_2 (2.9 ml, 56.40 mmol) was added drop wise to a solution of Me_2NH (7.5 ml of a 7.9 M solution in water, 58.0 mmol) and NaOH (4.50 g, 113.00 mmol) in 50 ml of water cooled to -20°C. The mixture was stirred for 30 minutes at this temperature and extracted with toluene (70 ml). The organic layer was separated and dried with $MgSO_4$ to give a yellow solution of Me_2NBr which was added to a solution of 2-phenyl-phenol (**a**, 8.50 g, 51.70 mmol) in toluene (250 ml) cooled to -20°C. The mixture was stirred for 1 hour at room temperature and the formation of a white solid was observed. After completion of the reaction, a solution of HCl (5%) was added (50 ml) and the organic layer was extracted with water (300 ml). After evaporation of the solvent, a yellow oil was obtained. This was filtered through silica gel (30 g, Hexane : CH_2Cl_2 1:1) to afford a colorless oil that, dissolved in hexane and cooled to -20°C overnight, forms white needle crystals (10.90 g, 85 % yield). The analytical data were consistent with the ones reported in literature.[23]

3-Bromo-2-Isopropoxybiphenyl (c): Compound **b (**10.00 g, 40.10 mmol) was dissolved in acetone and NaOH (1.70 g, 42.20 mmol) was added as a solid. The solution was refluxed until almost complete dissolution of the base was observed and then 2- bromopropane (9.5 ml, 100.0 mmol) was added in portions with a syringe. The obtained solution was refluxed until completion of the reaction (around 18 h). It was cooled to room temperature and water (100 ml) was added followed by diethyl ether (200 ml). The organic layer was washed with brine (100 ml), separated, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil that was filtered through silica (30 g, Hexane: CH_2Cl_2 20:1) to afford 10.2 g of the desired compound **c**. 1H NMR ($CDCl_3$, 400 MHz): δ 7.55 (m, 3H), 7.42 (m, 2H), 7.35 (m, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 3.95 (sept, J = 7.6 Hz, 1H), 1.05 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): 152.6, 138.9, 137.8, 132.7, 130.5, 129.4, 128.4, 127.6, 124.9, 119.6, 76.4, 22.25. MS (EI) m/z calculated for $C_{15}H_{15}OBr$ (M+) 291.2, observed 292.2 [M+1].

2-Isopropoxybiphenyl-3-carbaldehyde (d): Compound **c** (5.35 g, 18.40 mmol) was dissolved in 100 ml of THF and cooled to -78°C. *n*-BuLi in hexane (20.20 mmol) was then added dropwise. The obtained solution was stirred for two hours at this temperature and then DMF (7.1 ml, 92.00 mmol) was slowly added via syringe. The reaction was stirred for 10 minutes and subsequently quenched by the addition of water (100 ml) followed by diethyl ether (200 ml). The organic layer was washed with brine, separated, dried over $MgSO_4$, filtered, and then concentrated to give a yellow oil. This was filtered through silica gel (40 g, Hexane : CH_2Cl_2 to only CH_2Cl_2) to give the desired product **d** (3.52 g, 79.8 %). The analytical data were consistent with the ones reported in literature.[24]

2-Isopropoxy-3-vinylbiphenyl (e): To a suspension of methyl-triphenylphosphonium bromide (6.30 g, 17.60 mmol) in 150 ml of THF was added NaOtBu (1.97 g, 20.60 mmol) as a solid in small portions. The obtained bright yellow mixture was stirred for 1 h at room temperature under nitrogen and then it was cooled to -78°C. **d** (3.50 g, 14.70 mmol) was added dropwise dissolved in 10 ml of THF. The reaction was

allowed to warm to room temperature, then quenched with water, followed by diethyl ether (100 ml). The organic layer was washed with brine, separated, dried over $MgSO_4$, filtered, and concentrated to give a colorless oil. Hexane (50 ml) was added and the immediate formation of a precipitate was observed. The supernatant hexane solution was decanted and the precipitate was washed twice with hexane (100 ml). Hexane fractions were then collected and dried to give a colorless oil. After filtering on a pad of silica gel (20 g, Hexane : CH_2Cl_2 9:1), the desired product **e** was obtained (3.44 g, 99 %). The analytical data were consistent with the one reported in literature.[25]

Procedures for metathesis reactions

Comments

-) Due to the low catalyst loading used, catalytic runs can be rather sensitive to impurities present in the substrates. For example, we find that ethyl acetate should be avoided as an eluent for the chromatographic purification of the substrates. Neat runs with substrates obtained in that manner were found to be less efficient.

-) The dependence of reaction concentration on the RCM activity is most probably not limited to Blechert-type precatalysts. In our first RCM study,[26] the time needed for **GII** to convert substrate **6** (RT, CH2Cl2) into the ring-closed product was taken from the literature (90 min for ca. 98% conversion at 0.01M).[27] In our more recent report,[12] we performed kinetic studies with **6** and **GII** and found that less than 20 minutes were needed for the reaction to go to >98% conversion (at 0.1M).

-) 1H NMR analysis of neat reaction runs with **GII** (see manuscript) contain 1-2% of an unidentified product that is neither the starting nor the final compound.

General procedure for kinetic study

A screw capped NMR tube was loaded in a glove box with the desired amount of

precatalyst dissolved in CH_2Cl_2 (stock solutions were always freshly prepared adding 10 ml of dry CH_2Cl_2 to 0.008 mmol of catalyst) and the solvent was dried. The diene (0.08 mmol) dissolved in CD_2Cl_2 (0.8 ml) was then added via syringe. Data points were collected after an appropriate period of time. The conversion was determined by comparing the ratio of the integrals of the methylene protons in the starting material with those in the product.

General procedure for neat reactions

A 1.5 ml screw capped scintillation vial was charged with the desired amount of precatalyst dissolved in CH_2Cl_2 and the solvent was removed in vacuum. A stirring bar was introduced into the vial and the desired amount of diene was added via syringe. Immediately, the color of the solution turns from transparent to pink and evolution of gas is observed. The reaction was followed by GC-MS analysis. When the reaction was completed an NMR of the crude mixture was recorded to determine the final conversion and the eventual presence of oligomers. The crude residue was then filtered on silica gel. For compounds in which the desired metathesis product was a solid (**6**, **8**, **9** and **13**) only moderate yields were observed (between 50 and 60 %) using this procedure.

General procedure for reaction in hexane solution

A 1.5 ml screw capped scintillation vial was charged with the desired amount of precatalyst dissolved in CH_2Cl_2 and the solvent was removed in vacuum. Hexane was then added and the resulting solution was added, via syringe, to a scintillation vial containing the desired amount of diene and a stirring bar. After a few seconds, formation of a white suspension was observed. Reaction conversion was followed by GC-MS (samples of the hexane solution were collected and the consumption of the starting material was observed). When the reaction was complete, diethyl ether was added and the solution was transferred into a round bottom flask. The solvent was evaporated and an NMR of the product was recorded to determine the final conversion and the eventual presence of oligomers.

Kinetic Data

Kinetic data for substrates **10**, **12-14** have been run with *anti*-**3** only (27°C, 0.1M CD_2Cl_2). With a catalyst loading of 0.1 mol%, reaction times were 1 min (**10**), 6 min (**12**) and 4 min (**13**).

Reaction curves

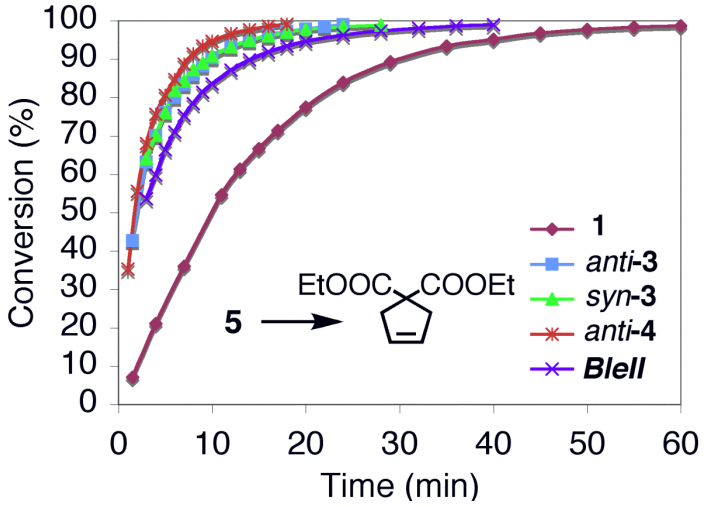


Figure S3. RCM of **5**, using 0.1 mol% of the respective catalysts (27°C, 0.1M, CD_2Cl_2).

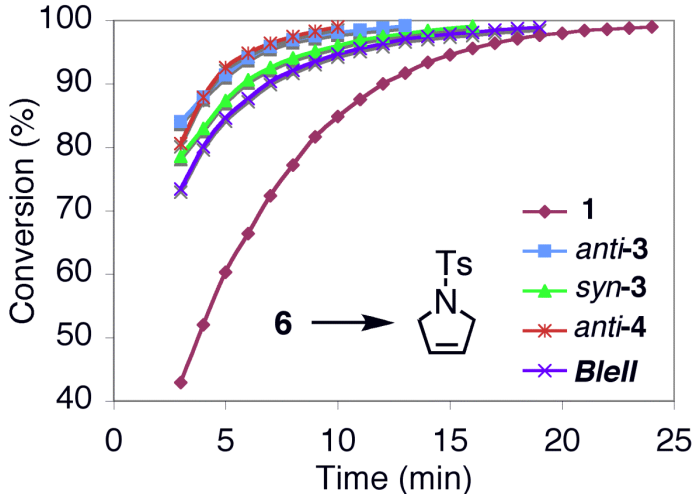


Figure S4. RCM of **6**, using 0.1 mol% of the respective catalysts (27°C, 0.1M CD_2Cl_2).

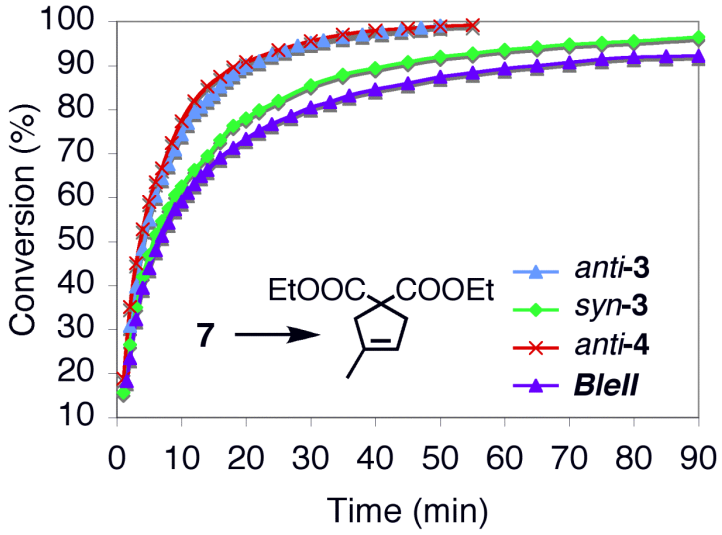


Figure S5. RCM of **7**, using 0.1 mol% of the respective catalysts (27°C, 0.1M CD_2Cl_2).

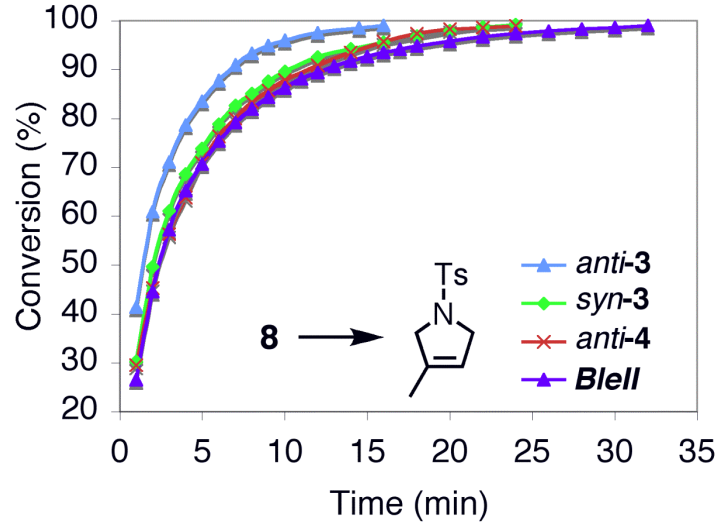


Figure S6. RCM of **8**, using 0.1 mol% of the respective catalysts (27°C, 0.1M CD_2Cl_2).

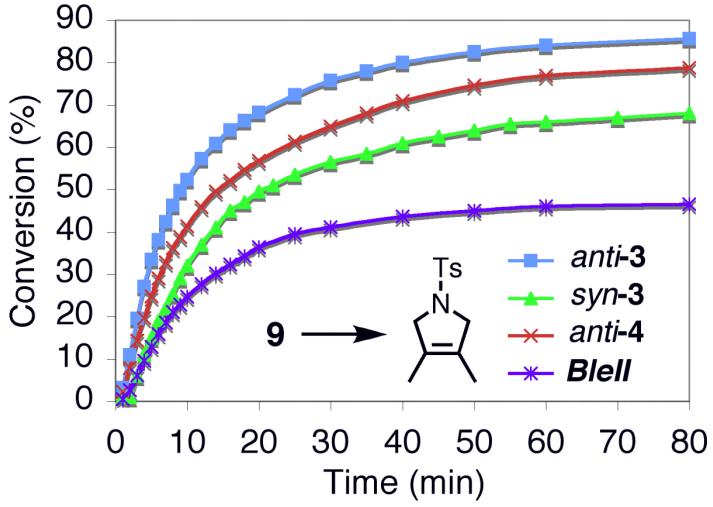


Figure S7. RCM of **9**, using 2 mol% of the respective catalysts (30°C, 0.1M CD_2Cl_2).

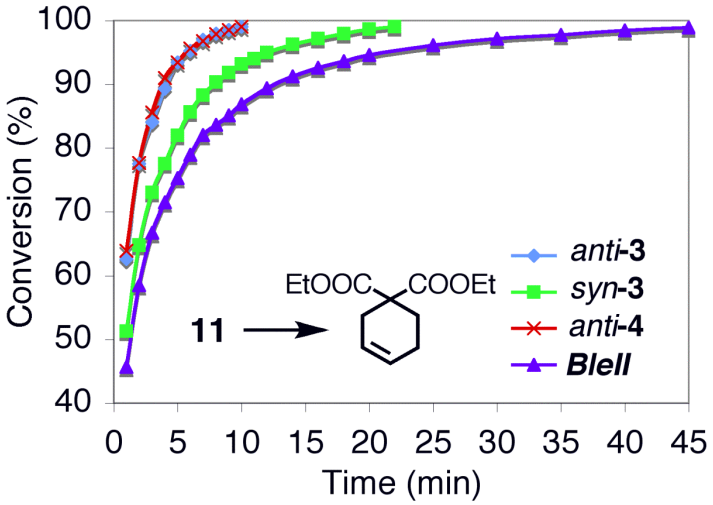


Figure S8. RCM of **11**, using 0.1 mol% of the respective catalysts (27°C, 0.1M CD_2Cl_2).

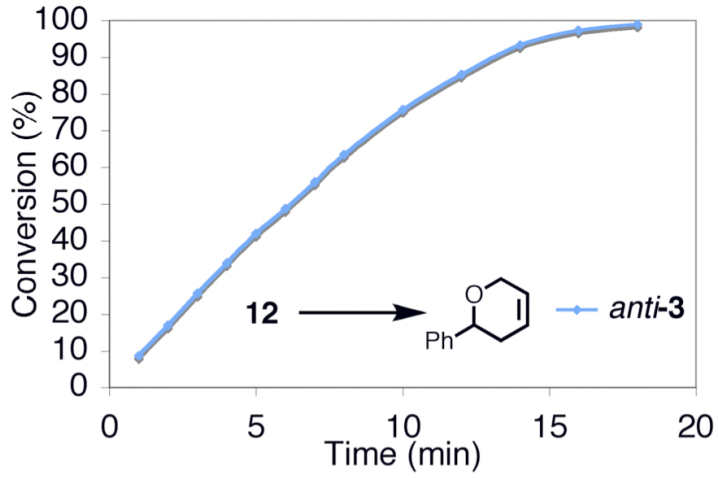


Figure S9. RCM of **14**, using 0.1 mol% of *anti*-**3** (27°C, 0.1M CD_2Cl_2).

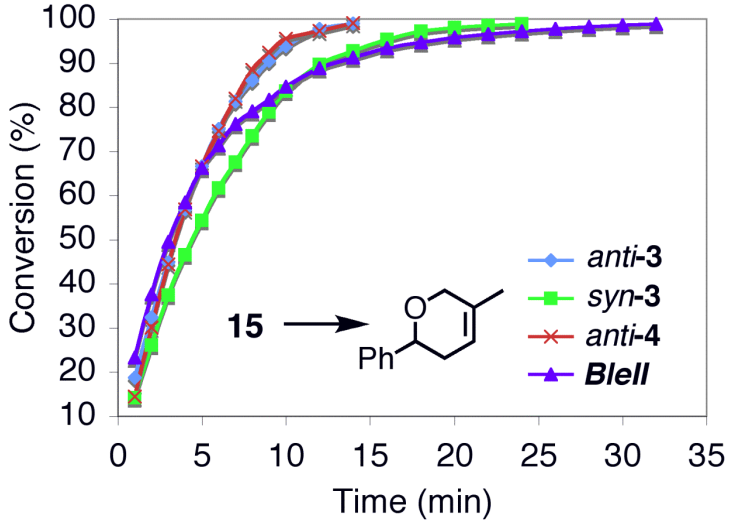


Figure S10. RCM of **15**, using 0.2 mol% of the respective catalysts (27°C, 0.1M CD_2Cl_2).

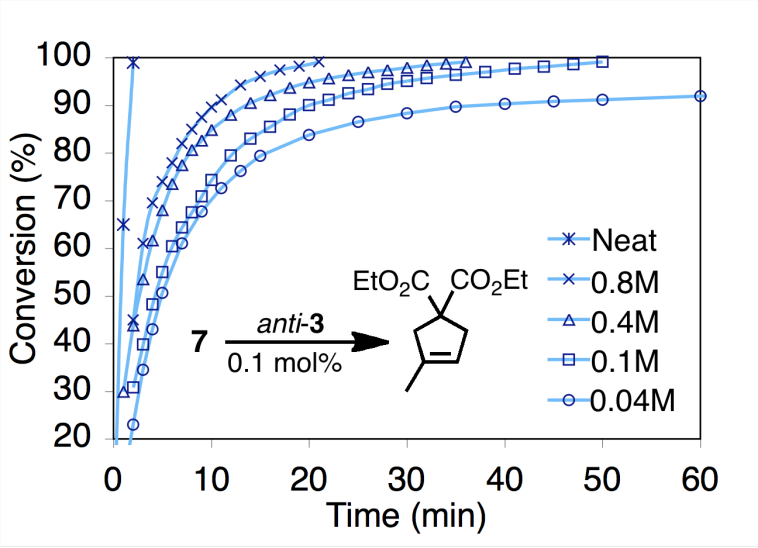
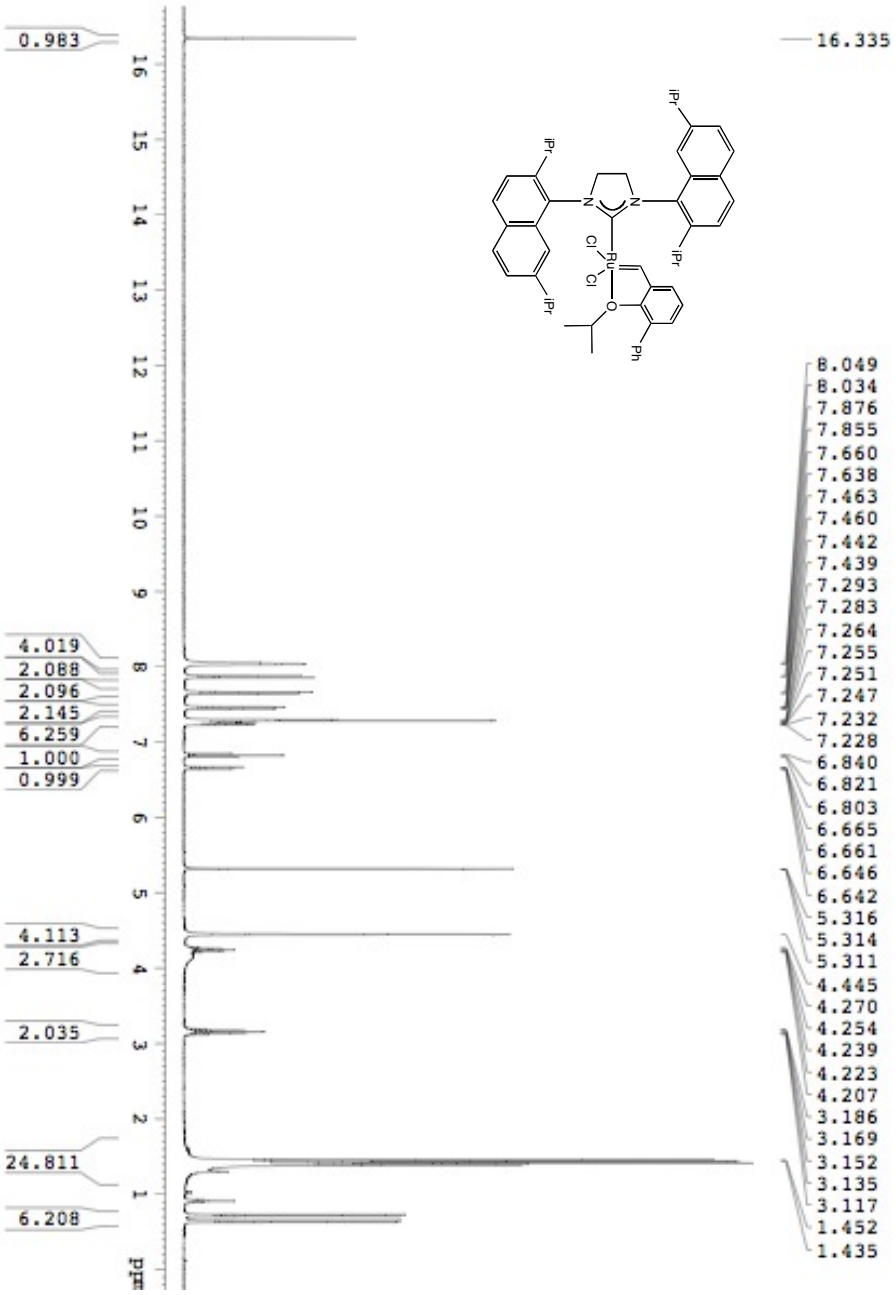


Figure S11. RCM of **7**, using 0.1 mol% of *anti*-**3** at different solvent concentrations (CD_2Cl_2) . For runs at 0.4M and 0.8M, ethylene formed during the reaction is released by piercing the screw-cap septum of the NMR tube every 3-5 minutes (the same procedure when applied for 0.1M has practically no effect on the outcome).

2.3 NMR Data


0.983
4.019
2.088
2.096
2.145
6.259
1.000
0.999
4.113
2.716
2.035
24.811
6.208
16.335
8.049
8.034
7.876
7.855
7.660
7.638
7.463
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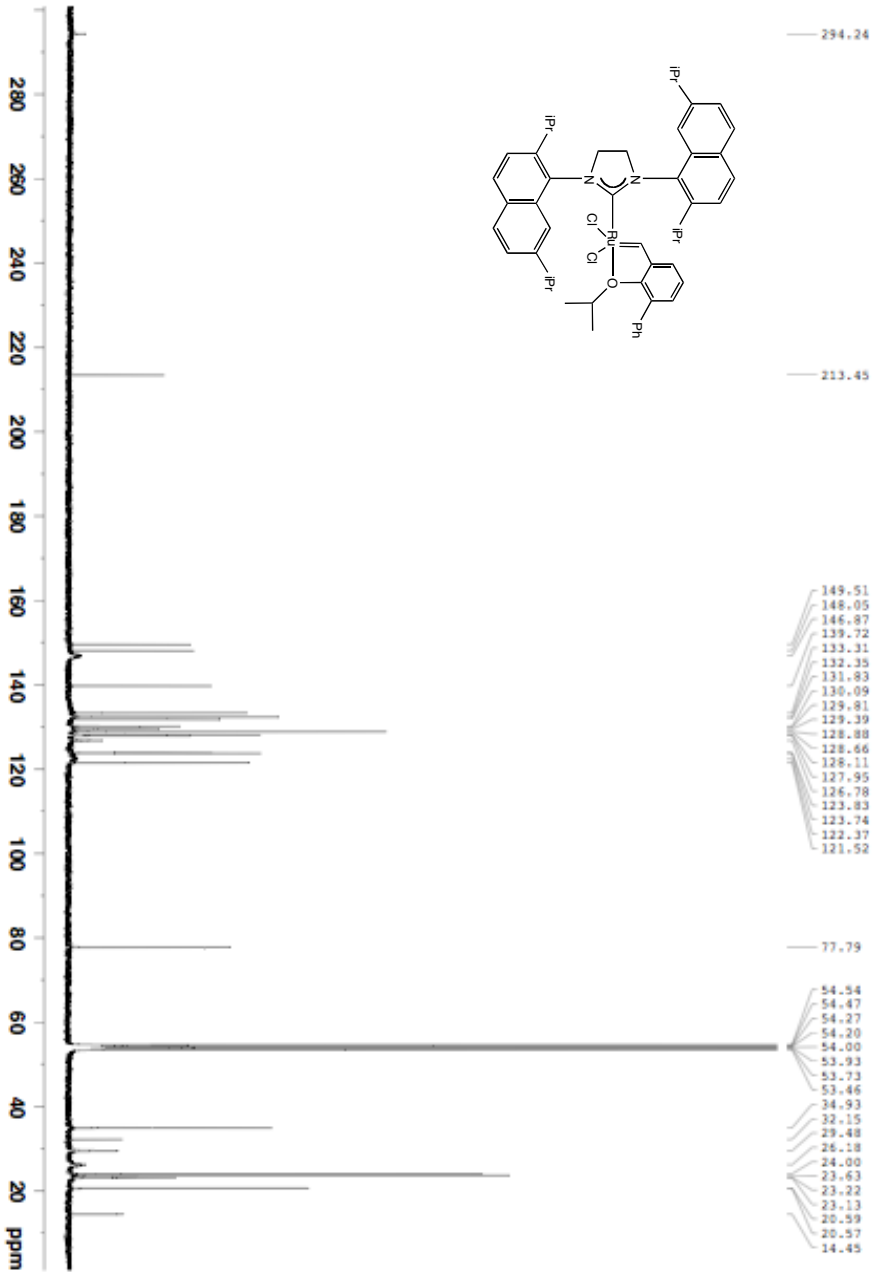
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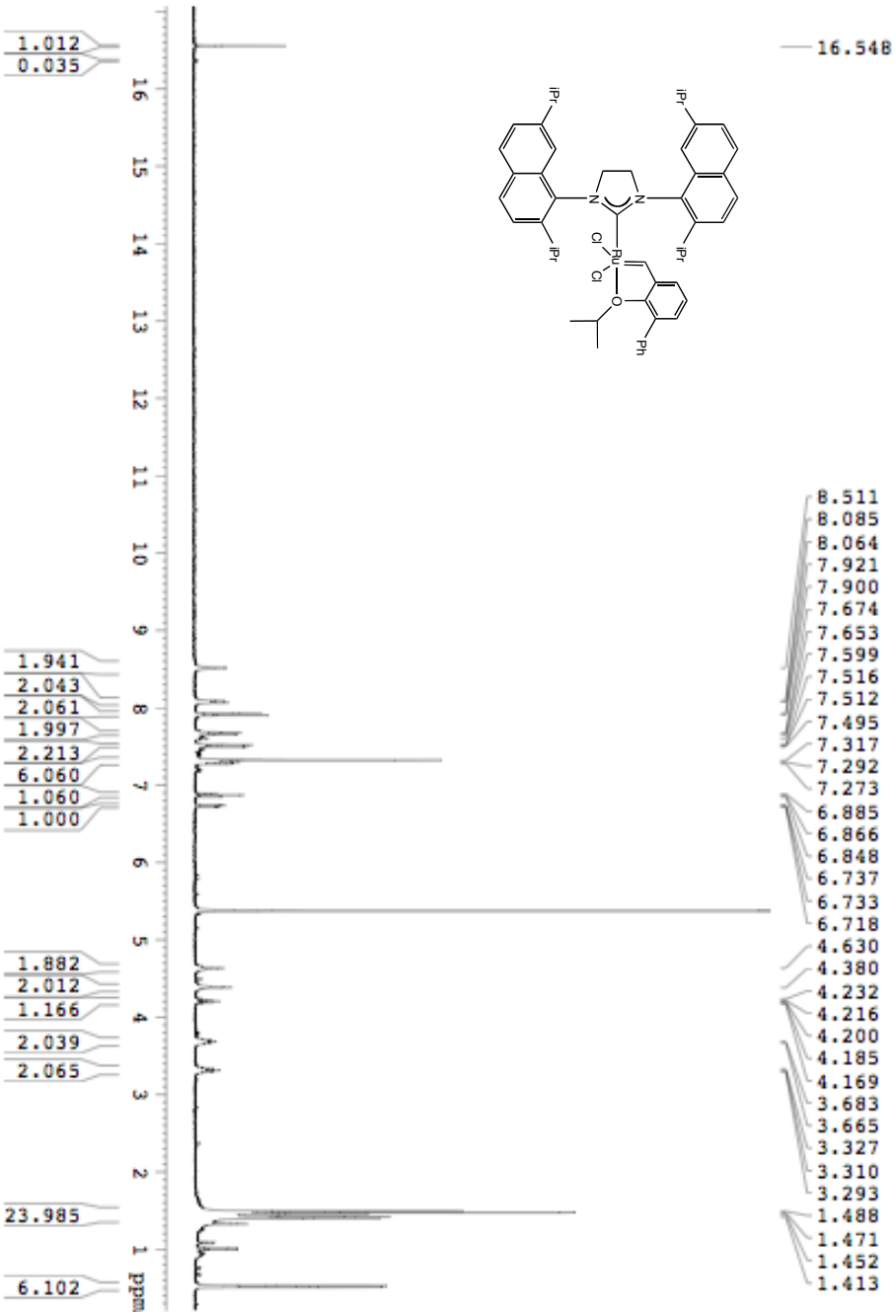
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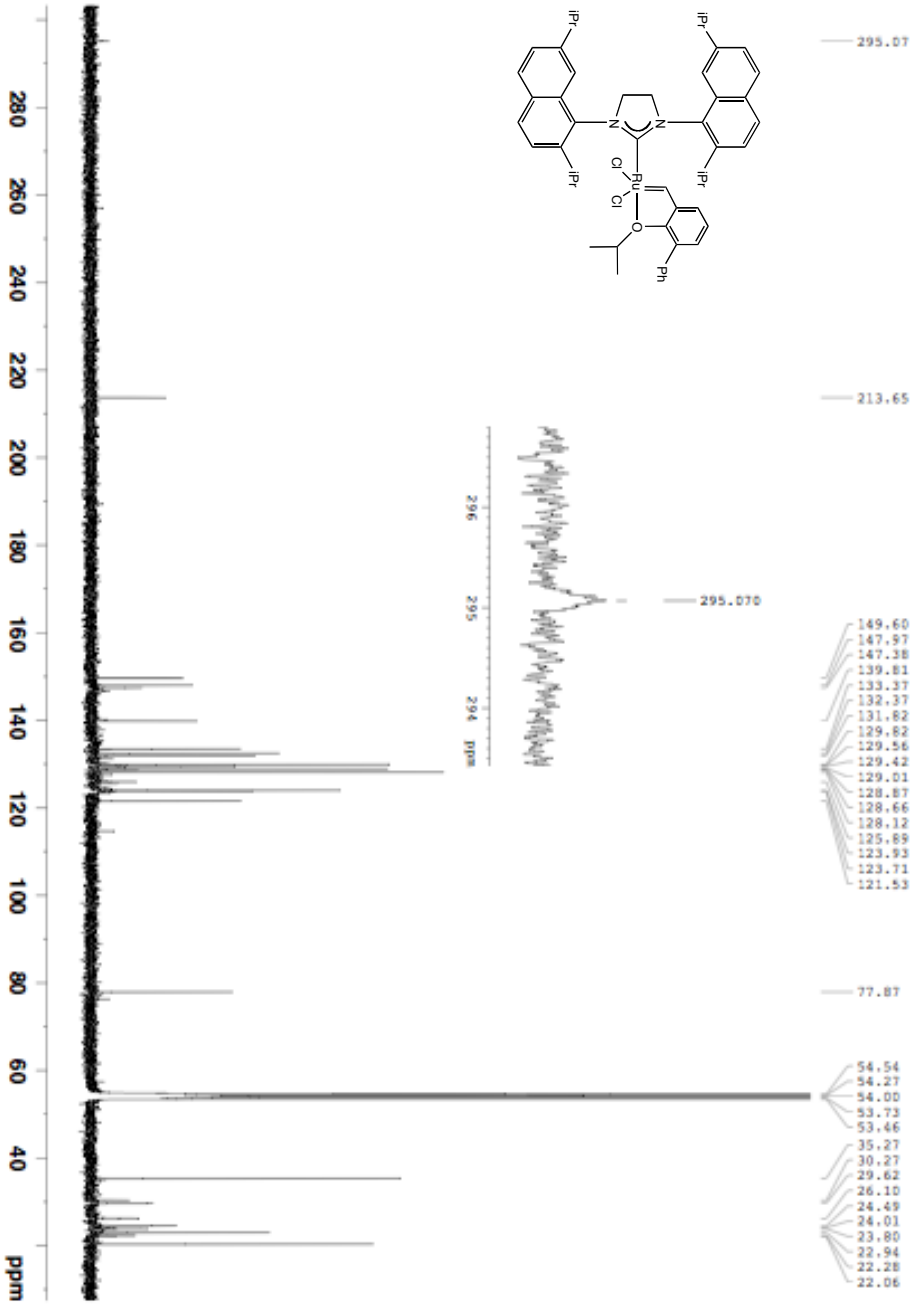
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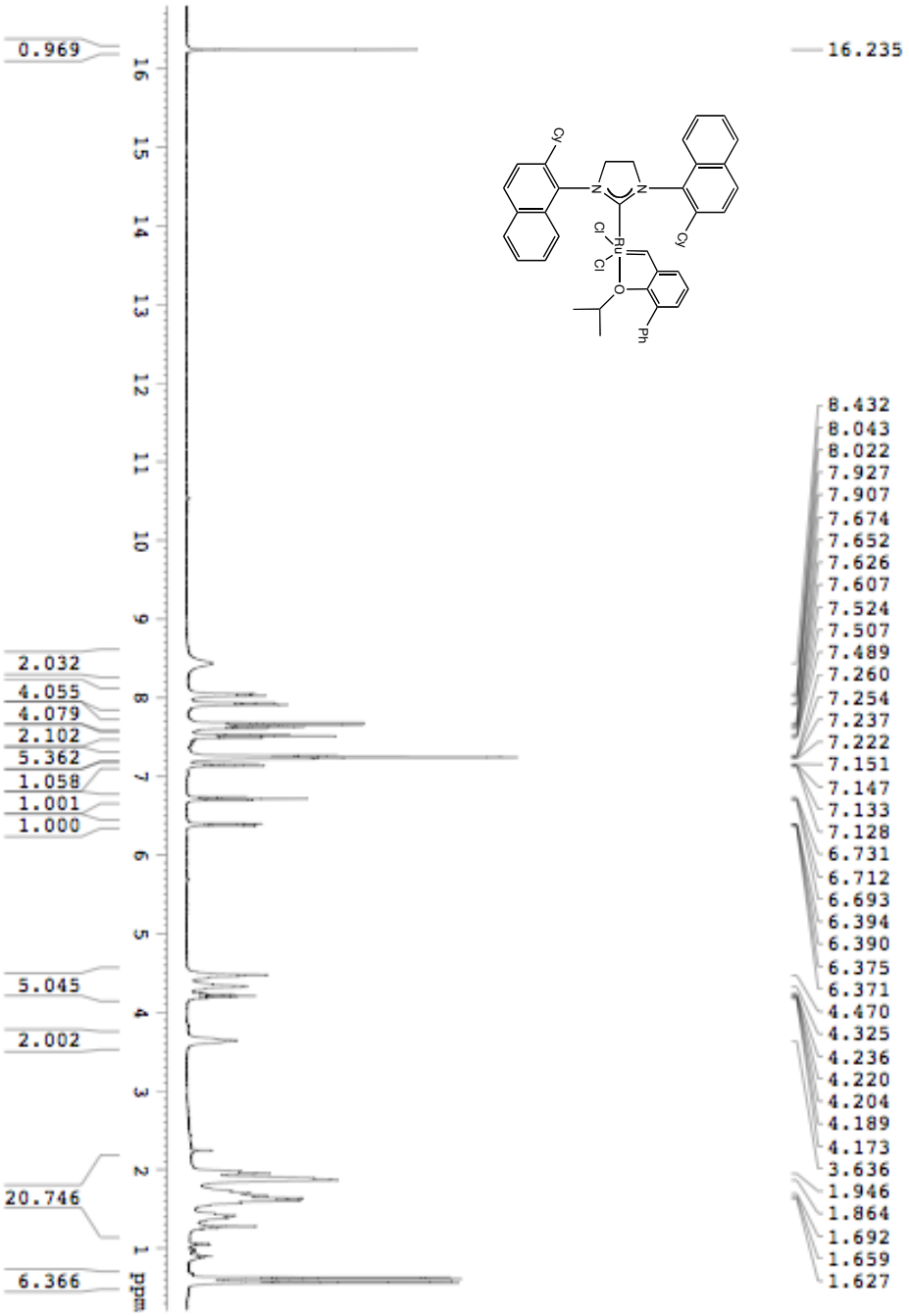
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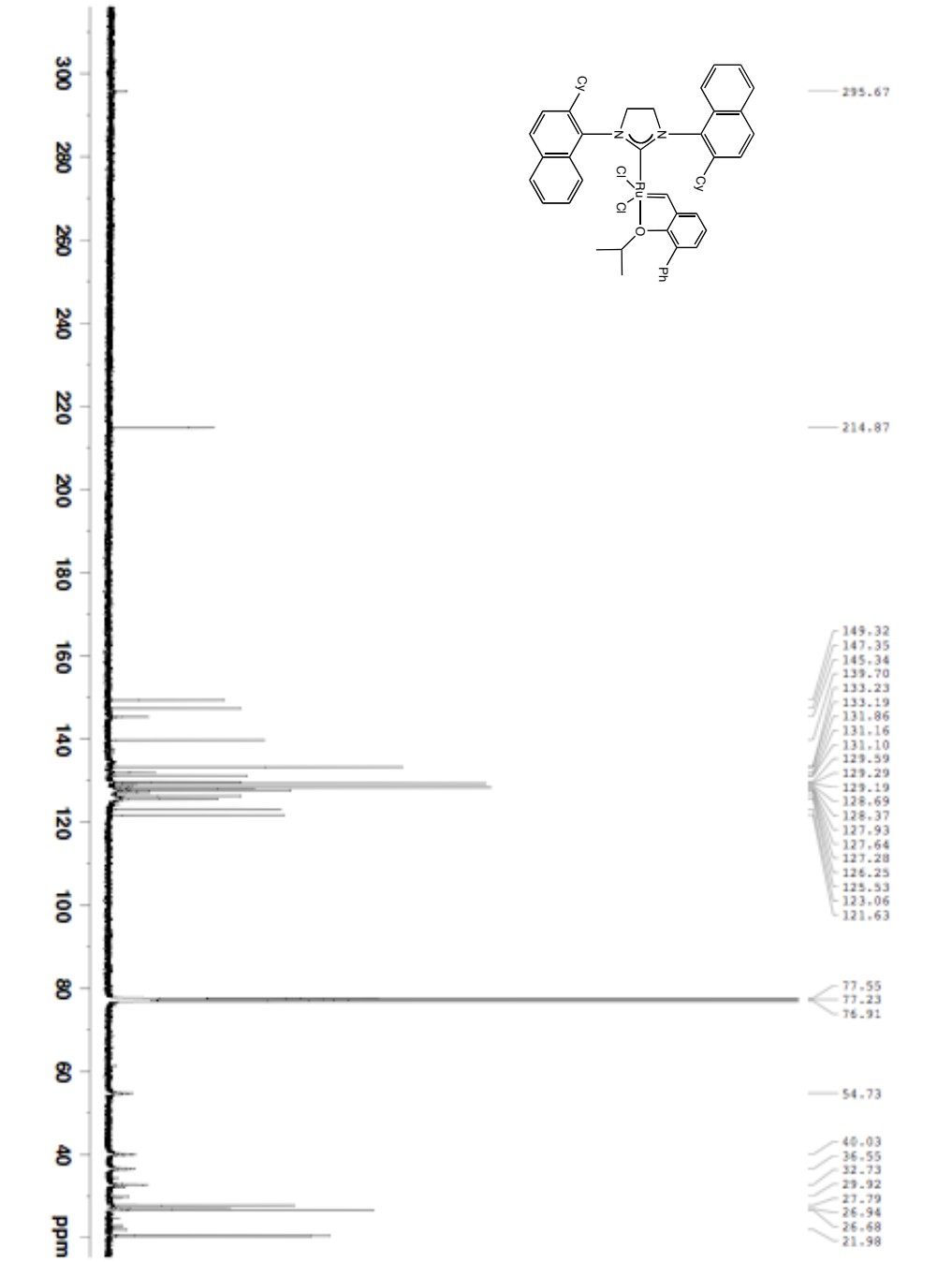
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131.86
131.16
131.10
129.59
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128.69
128.37
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127.64
127.28
126.25
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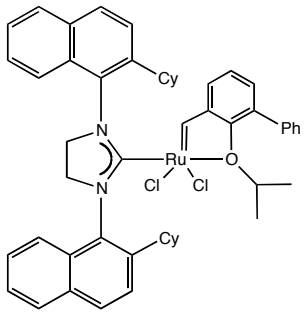
121.63
77.55
77.23
76.91
54.73
40.03
36.55
32.73
29.92
27.79
26.94
26.68
21.98
300
280
260
240
220
200
180
160
140
120
100
80
60
40
ppm

2.4 Additional experimental data

General procedure for the improved one-pot synthesis of the catalyst:

In a glovebox the desired carbene (1 eq) was dissolved in toluene and **GI** was added (1 eq). The obtained dark violet solution was stirred for 24 h and then the conversion was checked via ^{31}P NMR. If the conversion was not complete after this time another 0.2 eq of carbene were added and the mixture was stirred until from ^{31}P NMR almost full conversion was obtained. The solvent was then evaporated and the obtained dark red foam was dried in high vacuum for 3 h. CuCl (3 eq), the desired styrene compound (3 eq) and dry CH_2Cl_2 (a 0.2 M solution was used) were then added and the obtained suspension was refluxed (43°C) for 1.5 h under nitrogen. The color of the reaction mixture became brown and then, upon completion of the reaction, dark green. The solvent was evaporated and the flask was transferred into the glovebox. The green foam was dissolved in 2 ml of CH_2Cl_2 and directly charged into a silica gel filter (1x15 cm). The solid obtained after chromatography was usually dissolved in the minimal amount of hexane (or Hexane-CH_2Cl_2) and then crystallized at -35 °C to eliminate the impurity residue.

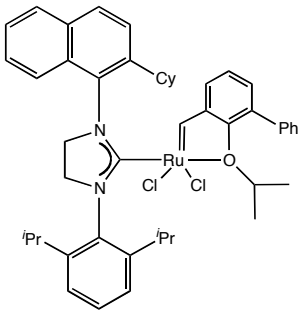
Catalyst *syn*-**4**:



Chromatography: Hexane to Hexane-CH_2Cl_2 to elute the styrene in excess; Hexane-CH_2Cl_2 to elute the first isomer (*anti*) and then only CH_2Cl_2 to obtain the second isomer (*sin*). Microcrystalline product obtained from fraction two cooling for 3 days at -35°C a concentrated solution of the catalyst in pentane. ^1H NMR (C_6D_6, 400 MHz): δ 16.55 (s, 1H), 8.82 (d, J = 8.6 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H), 7.75 (m,

4H), 7.62 (d, J = 8.6 Hz, 3H), 7.39 (m, 1H), 6.95-6.85 (m, 4H), 6.68 (m, 1H), 6.48 (m, 1H), 4.45 (hept, J = 6.2 Hz, 1H), 4.00-3-65 (m, 6H), 2.20-0.90 (m, 20H), 0.85 (d, J = 7.8 Hz, 6H). ^{13}C NMR (C_6D_3, 100 MHz): δ 292.8, 292.7, 215.3, 149.9, 148.3, 140.2, 134.0, 133.1, 131.9, 130.9, 130.2, 129.8, 129.7, 129.5, 128.8, 128.7, 128.6, 128.0, 127.9, 127.5, 126.8, 125.8, 124.2, 123.6, 121.5, 78.0, 75.1, 31.2, 30.8, 28.7, 27.5, 27.4, 27.2, 26.8, 22.5, 20.7. Elemental analysis calculated for $C_{51}H_{54}N_2O_1Cl_2Ru_1$: C 69.37, H 6.16, N 3.17; found C 68.16, H 6.49, N 2.63.

Catalyst **16**:



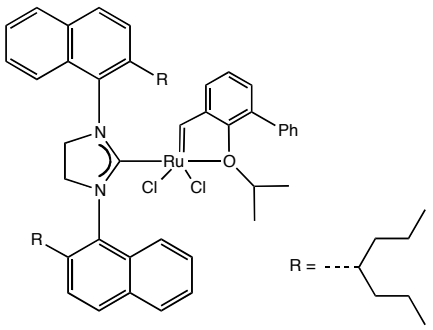
Chromatography: Hexane to Hexane-CH_2Cl_2 to elute the styrene in excess. Only CH_2Cl_2 to elute the product. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 16.50 (s, 1H), 8.61 (d, J = 8.2 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.65 (m, 3H), 7.45 (m, 3H), 7.32-7.18 (m, 6H), 6.87-6.74 (m, 2H), 4.50-4.20 (m, 5H), 3.82 (s, broad, 1H), 3.48 (s, broad, 1H), 3.32 (s, broad, 1H) 2.0-0.8 (m, 22H), 0.70-0.50 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 295.1, 294.9, 214.0, 149.4, 149.1, 147.5, 145.9, 139.7, 133.3, 133.2, 131.4, 131.2, 130.3, 129.7, 129.4, 129.1, 128.3, 128.2, 127.7, 127.4, 126.5, 126.0, 125.2, 125.0, 124.9, 123.1, 121.6, 55.4, 53.8, 40.7, 37.2, 34.9, 34.7, 34.3, 32.1, 31.8, 28.7, 28.5, 27.9, 27.1, 26.9, 26.7, 25.5, 24.0, 23.9, 22.8, 22.5, 22.3, 20.9, 20.5, 20.3, 14.3, 14.2. HRMS (ESI) calculated for $C_{47}H_{54}N_2O_1Cl_2Ru_1$: 834.2656. Found 799.2977 $[M\text{-}Cl]^+$. Elemental analysis calculated for $C_{47}H_{54}N_2O_1Cl_2Ru_1$: C 67.61, H 6.52, N 3.36; found C 64.89, H 6.27, N 3.16.

Catalyst **17**

Chromatography: Hexane to Hexane-CH_2Cl_2 8:1 to elute the styrene in excess.

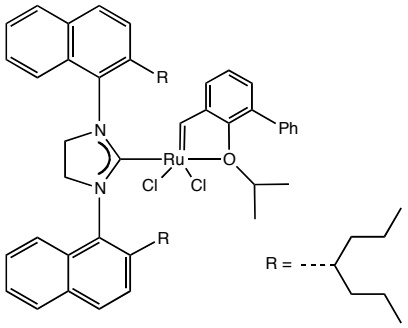
Hexane-CH_2Cl_2 1:1 to elute the first isomer (*anti*). Only CH_2Cl_2 was used to elute the second isomer.

anti-**17**



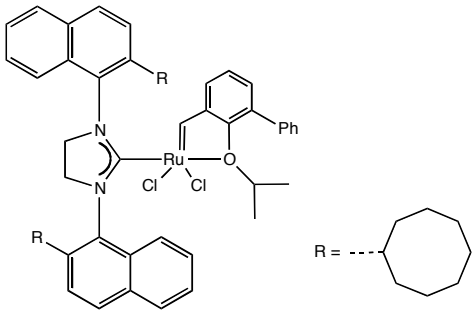
Crystals suitable for X-Ray diffraction were obtained by slow evaporation of a mixture of catalyst in Hexane-CH_2Cl_2. ^{1}H NMR (C_6D_6, 400 MHz): δ 16.50 (s, 1H), 8.68 (d, *J* = 8.7 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.70 (t, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.35 (m, 4H), 6.95 (m, 4H), 6.60 (m, 1H), 6.50 (m, 1H), 4.45 (m, 1H), 4.00 (m, 6H), 2.20-0.80 (m, 34H). ^{13}C NMR (C_6D_6, 100 MHz): δ 291.6, 291.5, 217.9, 150.5, 148.4, 140.5, 140.1, 134.0, 132.8, 132.6, 132.2, 130.1, 129.8, 129.4, 128.9, 128.0, 127.7, 127.5, 126.7, 126.2, 126.0, 123.6, 121.1, 78.3, 76.6, 54.9, 40.3, 39.0, 32.3, 27.6, 23.4, 22.6, 22.5, 21.8, 20.8, 20.7, 15.5, 15.4, 14.7. HRMS (ESI) calculated for $C_{51}H_{58}N_2O_1Cl_2Ru$: 914.3282. Found 879.3598 $[M-Cl]^+$. Elemental analysis calculated for $C_{51}H_{58}N_2O_1Cl_2Ru_1*H_2O$: C 68.22, H 6.91, N 3.00; found C 68.42, H 6.89, N 3.01.

syn-**17**



^{1}H NMR (C_6D_6, 400 MHz): δ 16.7 (s, 1H), 8.98 (d, *J* = 8.6 Hz, 2H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.78 (m, 4H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.38 (m, 4H), 6.98 (m, 4H), 6.68 (m, 1H), 6.52 (m, 1H), 4.43 (m, 1H), 4.04 (s, broad 4H), 3.80 (s, broad, 2H), 2.00-0.80 (m, 34H). ^{13}C NMR (C_6D_6, 100 MHz): δ 292.2, 292.0, 216.2, 150.5, 148.3, 140.1, 134.0, 132.8, 132.2, 129.8, 129.5, 128.8, 128.0, 127.5, 127.0, 126.3, 123.6, 121.2, 78.4, 54.9, 40.2, 39.8, 38.3, 22.5, 21.8, 20.7, 15.5, 15.3. HRMS (ESI) calculated for $C_{51}H_{58}N_2O_1Cl_2Ru$: 914.3282. Found 879.3598 $[M\text{-}Cl]^+$. Elemental analysis calculated for $C_{51}H_{58}N_2O_1Cl_2Ru_1$: C 69.57, H 6.83, N 3.06; found C 69.00, H 6.74, N 3.04.

Catalyst *anti*-**18**



^{1}H NMR (C_6D_6, 400 MHz): δ 16.55 (s, 1H), 8.65 (s, broad, 2H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.70 (m, 4H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.35 (t, *J* = 5.6 Hz, 2H), 7.17 (2H, overlapped with solvent signal) 6.85 (m, 4H), 6.55 (m, 1H), 6.42 (m, 1H), 4.37 (hept, *J* = 6.2 Hz, 1H), 4.15-3.70 (m, 6H), 2.20-1.60 (m, 20H), 0.75 (d, *J* = 7.8 Hz, 6H). ^{13}C NMR (C_6D_6, 100 MHz): δ 293.2, 293.1, 216.3, 150.1, 150.0, 148.4, 140.1, 133.8, 133.1, 132.2, 132.0, 130.1, 130.0, 129.5, 128.9, 128.8, 128.7, 127.6, 126.6, 126.3,

126.0, 123.6, 121.3, 78.1, 76.5, 39.5, 28.1, 27.0, 22.6, 20.7, 20.6. Elemental analysis calculated for $C_{55}H_{62}N_2O_1Cl_2Ru_1$: C 70.35, H 6.65, N 2.98; found C 70.17, H 6.63, N 2.98.

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[7] The results seem counterintuitive given the overall higher steric bulk of (2,7)-SIPrNap and (2)-SICyNap compared to SIMes (ref 3a).We believe that this is due to

the fact that one of the sides on the naphthyl moieties is more open than in SIMes and, as a consequence, bulky substrates can approach the metal center more easily.

[8] To our knowledge, this is the first study relating reactivity to reaction concentration since productive RCM was introduced. Early studies on substrates such as **5** with less selective/active Schrock's and Grubbs' I catalysts showed that productive RCM needed dilutions of at least 0.1 M; see: (a) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978. (b) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. For more recent relevant reports, see: (c) Dinger, M. B.; Mol, J. C. *Adv. Synth. Catal.* **2002**, *344*, 671. (d) Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **2002**, *124*, 6991. (e) Maifeld, S. V.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 12228.

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[10] Grela and more recently Grubbs showed that high TONs can be achieved when heating **5** in toluene with **HovII**. However, already **7** gives much poorer results: (a) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. Eur. J.* **2008**, *14*, 806. (b) Kuhn, K. M.; Bourg, J.-P.; Chung, C. K.; Virgil, S. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2009**, *131*, 5313.

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[21] Synthesized starting from 4-phenyl-1-buten-4-ol and 4-bromo-2-methyl-2-butene with the same procedure reported for the synthesis of compound **15**.

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CHAPTER THREE

The effect of substituents on the *syn-anti* conformer ratio in naphthyl-based imidazolinium salts and their corresponding *N*-heterocyclic carbenes

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Dedicated to Prof. Dr. Heinz Heimgartner, a true gentleman, on the occasion of his 70th birthday

(Arkivoc, **2011**, *vi*, 176*)*

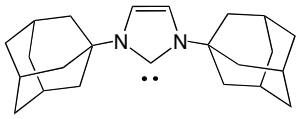
3.1 Abstract

Eight new *N*-heterocyclic carbenes (NHCs) featuring substituted naphthyl side chains were synthesized. These molecules are present in solution as a stable mixture of *anti* and *syn* conformers. Through careful tuning of the substituents on position 2 and 2,7 of the naphthyl side chains, it was possible to synthesize molecules that display a strong preference for the *anti* conformation (up to 95:5). This will greatly facilitate their optimized use as single isomeric ligands in metal-catalysis and as organocatalysts on their own.

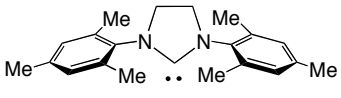
3.2 Introduction

The affirmation of N-heterocyclic carbenes as ligands for transition metals catalysts and as organic catalysts proved to be an important innovation in the field of catalysis.[1,2] Especially useful in this respect (so far) have been N-heterocyclic carbenes with five-membered heterocyclic structures first reported by Arduengo et al., such as imidazol-2-ylidene **A** and the saturated heterocyclic imidazolidin-2-ylidene

derivatives **B**.[3,4]



A



B

Whereas dozens of structural variations of NHCs **A** and **B** exist nowadays, the overwhelming majority incorporates the unsaturated central N-heterocycle of **A**. The reason for this lies in the surprisingly different stabilities of unsaturated and saturated NHCs. While dimerization of aromatically stabilized N-heterocyclic carbenes of type **A** is thermodynamically unfavorable even for small N-substituents like R = Me,[5,6] formation of the enetetramine dimer of **B** occurs readily. This renders saturated NHCs considerably less amenable to catalysis and restricts access to stable modifications of this ligand class, as the substituents at the nitrogen atoms need to be very bulky. The demarcation line separating stable from unstable carbenes may be established and lies somewhere between ^{t}Bu/^{i}Pr for N-alkyl substituents and Mes/Ph for aromatic side chains.[7,8,9]

In catalysis, work in the last decade has shown that monodentate NHCs with bulky, aryl-substituted side chains are the overall most successful design. As such, 2,4,6-mesityl-substituted IMes and 2,6-isopropylphenyl-substituted IPr and their saturated imidazolin-2-ylidene counterparts (SIMes and SIPr) still remain the only ligands that represent a truly viable alternative to phosphines, in terms of both versatility and reactivity.

Our entry in this fascinating field of research began with the design and the synthesis of stable saturated free carbenes that feature substituted naphthyl side chains.[10] We reasoned that this architecture would mimic well the original SIMes and SIPr ligand systems, offering at the same time a scaffold that is less hindered in proximity to the potential metal binding site and that can be functionalized more readily with a wide range of substituents, tuning both its steric and electronic properties. The substitution pattern confers to these molecules a high degree of conformational stability, generating in solution a mixture of *anti* and *syn* conformers (Figure 1).

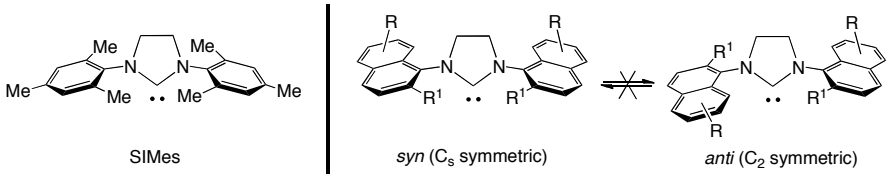


Figure 1. Imidazolin-2-ylidenes with phenyl (left) and naphthyl (right) side chains.

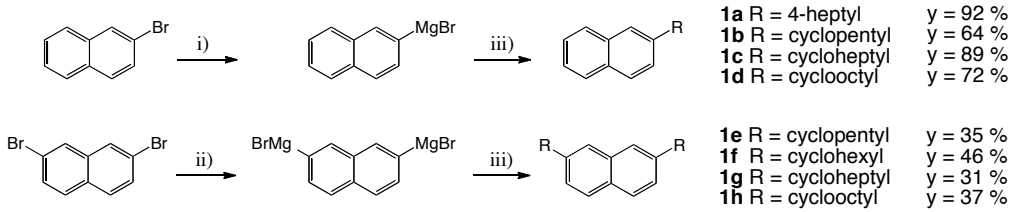
Detailed NMR study on the fluxional behavior of this class of carbenes showed that, even at high temperature, interconversion between the conformers is not possible if sterically demanding substituents are present in position 2 of the naphthyl side chains (R^1 in Figure 3.1).[11] This encouraged us to attempt the separation of the *syn* and *anti* isomers for some of these molecules but this process, up to now, has been successful only when the NHC was incorporated into a stable metal complex. Recent studies performed in our laboratory also indicated that, for some type of metal-catalyzed transformations, organometallic catalysts containing NHCs in the *anti* isomeric form perform better then the ones in the *syn* form.[12]

These reasons prompted us to attempt the synthesis of molecules displaying a conformational preference for only one of the two isomers. Herein, we describe the synthesis of a series of new saturated NHCs that incorporate alkylated naphthyl side chains. With the aim of minimizing the formation of the *syn* isomer, we selected a bulky, linear alkyl substitutent as well as more rigid, cyclic alkyl derivatives of various sizes

3.3 Results and Discussion

Synthesis of free NHCs began with the preparation of mono and dialkylated naphthalene rings. Compounds **1a-d** were obtained starting from 2-bromonaphthalene and the desired alkyl halide via an iron-catalyzed C_{sp2}-C_{sp3} coupling adapting a procedure reported recently by Cahiez et al. (Scheme 2).[13] After initial formation of the mono-Grignard derivative of naphthalene, the solution/suspension was added to the respective alkylbromide solution in THF containing the $(FeCl_3)_2(TMEDA)_3$ catalyst (4.6 mol% Fe).

Scheme 1. General synthesis of new 2- and 2,7-substituted naphthalenes.



1a R = 4-heptyl y = 92 %
1b R = cyclopentyl y = 64 %
1c R = cycloheptyl y = 89 %
1d R = cyclooctyl y = 72 %

1e R = cyclopentyl y = 35 %
1f R = cyclohexyl y = 46 %
1g R = cycloheptyl y = 31 %
1h R = cyclooctyl y = 37 %

Reaction conditions: i) Mg, THF, I_2 (cat.), r.t. ii) Mg, THF, I_2 (cat.), reflux 2h;
iii) $(FeCl_3)_2(TMEDA)_3$ (cat.), THF, RBr

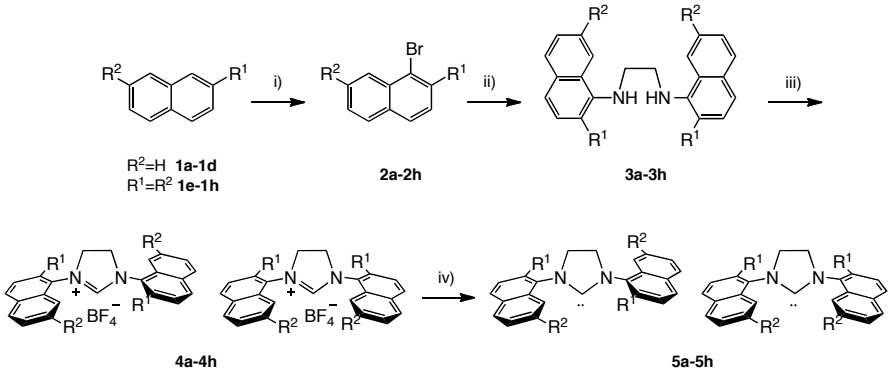
After appropriate aqueous workup, elimination of naphthalene, the main byproduct of the reaction, was easily achieved via sublimation under high vacuum. The reaction proceeded in all cases with good yields, apparently unaffected by the increasing bulkiness of the alkyl halide employed (Scheme 1).

Compounds **1e-h** were obtained in a similar manner, starting from 2,7-dibromonaphthalene.[14] Generation of the di-Grignard reagent, required for the subsequent coupling reaction, proceeded without problems when heating a THF solution at reflux temperature for several hours. The resulting di-Grignard compound can be used directly as a heavy suspension in THF or it can be isolated under nitrogen as a white stable powder after evaporation of the solvent. The di-Grignard is then slowly added (as powder or as suspension) to the mixture of catalyst (7 mol% Fe) and alkyl bromide, resulting in a rapid color change of the reaction to dark brown/black and this color was maintained upon completion of the reaction. After standard aqueous work up,[15] the final purification of the product was performed via bulb-to-bulb high vacuum distillation (Kugelrohr) to separate the desired product from the monoalkylated naphthalene compound (the main secondary product of the reaction) and from naphthalene. This purification method allowed to easily scale-up the reaction to (at least) 10 grams. The isolated yields were generally not very high (35 to 45 %), but the reaction procedure proved to be robust and suitable for a wide range of commercially available bromoalkanes. Indeed and to the best of our knowledge, these are the first examples reported in the literature of an iron-catalyzed double Kumada-type C_{sp2}-C_{sp3} coupling.

Bromination of the alkylnaphthalenes (Scheme 2) was achieved in all cases with excellent yield and with perfect regioselectivity for position 1 of the naphthalene

when performing the reaction at low temperature (-78 °C) using equimolar amounts of Br_2 with CH_2Cl_2 as the solvent.[16] The control of the temperature is particularly important for 2-alkylnaphthalenes; when the reaction is performed at 0 °C, a mixture of regioisomers is obtained whose separation by column chromatography is not trivial.[17] Quenching of the reaction involved addition of a diluted aqueous solution of NaOH to the reaction solution at -78 °C, as the more commonly used $Na_2S_2O_3$ agent was found to sometimes interfere with the subsequent metal-catalyzed reaction step. This double Buchwald-Hartwig coupling with ethylenediamine in the presence of $Pd_2(dba)_3$ (mol%), (±)-BINAP (10 mol%) and NaO^{t}Bu (eq) generated diamines **3a-h** in good yield and high purity after chromatographic purification.

Scheme 2. General synthesis of the free NHCs featuring naphthyl side chains.



Reaction conditions: i) Br_2, CH_2Cl_2, -78°C; ii) ethylenediamine, $Pd_2(dba)_3$, *rac*-BINAP, NaO^{t}Bu, toluene, 110°C; iii) NH_4BF_4, HCO_2H (cat.), $HC(OEt)_3$, 100°C, iv) NaH, KO^{t}Bu (cat.), THF.

Finally, following the procedure originally reported by Grubbs et al.,[18] ring-closing of the respective diamines in the presence of triethyl orthoformate as reagent/solvent and NH_4BF_4 furnished the desired imidazolinium salts **4a-h** in generally good yields. Table 1 reports the yields for the ring formation step and the ratio of conformers (*syn* respectively *anti*) observed. To have a more general overview, data concerning naphthyl-based NHC salts already reported by our group are also shown.

Tendentially, yields are slightly lower when starting with diamines that contain very bulky substituents in position 2 of the naphthalene moiety (Table 1, entries 1-7)

and with precursor molecules with 2,7-dialkylated precursors (Table 1, entires 8-13), probably reflecting an increasingly difficult approach of the nucleophile in the reaction sequence.

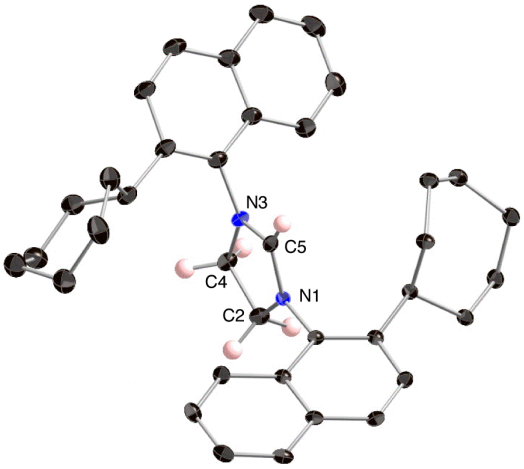
Concerning the *syn*/*anti*-ratio of the NHC salts, we note that when small alkyl groups and linear, flexible alkyl chains are present in positions 2 or 2,7 of the naphthalene rings (entries 1-3 and 8-9 in Table 1), the two possible conformers were formed in almost equal amounts. The same trend was observed when a small, cyclic ring was present in position 2 or 2,7 (entry 4 and 10 in Table 1). Increasing progressively the bulkiness of the cyclic alkyl substituents (entries 5-7 in Table 1) favors the formation of the *anti* conformer. When large cyclic alkyl groups are present in both positions 2 and 7, the *syn* conformer becomes strongly disfavored and, in the best case (entry 11), a 95:5 *anti*-*syn* ratio is obtained.

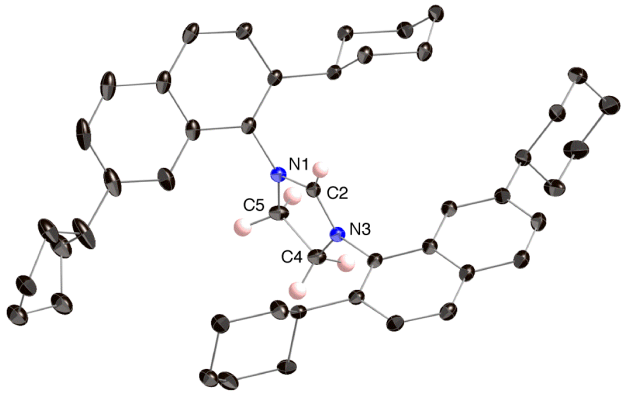
Table 1. Yields and *syn-anti* ratio for compounds **4a**-**4h** and previously reported imidazolinium salts containing naphthalene wingtips.

entry	imidazolinium salt	yield (%)	*syn-anti* ratio[a]
1	(2)-SIMeNap·HBF_4[b]	88	50 : 50
2	(2)-SIPrNap·HBF_4[b]	60	50 : 50
3	(2)-SIHeptNap·HBF_4 (**4a**)	75	43 : 57
4	(2)-SICypentNap·HBF_4 (**4b**)	75	50 : 50
5	(2)-SICyNap·HBF_4[b]	78	27 : 72
6	(2)-SICyheptNap·HBF_4 (**4c**)	58	22 : 78
7	(2)-SICyoctNap·HBF_4 (**4d**)	60	17 : 83
8	(2,7)-SIMeNap·HBF_4[b]	80	50 : 50
9	(2,7)-SIPrNap·HBF_4[b]	56	50 : 50
10	(2,7)-SICypentNap·HBF_4 (**4e**)	35	50 : 50
11	(2,7)-SICyNap·HBF_4 (**4f**)	50	5 : 95
12	(2,7)-SICyheptNap·HBF_4 (**4g**)	48	15 : 85
13	(2,7)-SICyoctNap·HBF_4 (**4h**)	29	10 : 90

[a] The ratios were deduced from NMR analysis. [b] These compounds have been reported before (ref. 10)

Finally and not surprisingly given our precedent studies, the NHC salts **4a-h** could be cleanly converted to free monomeric NHCs **5a-h** (Scheme 3), via deprotonation of the imidazolinium proton in THF with NaH in the presence of a catalytic amount of potassium *tert*-butoxide. ^{1}H NMR spectroscopy at 300 K of carbenes **5a-h** revealed two sets of signals corresponding, within error, to the ratio of *anti*/*syn* isomers found in the starting imidazolinium salts. This in turn means that a sufficiently high barrier to rotation between the conformers exists and that no interconversion occurs during and after the deprotonation step.





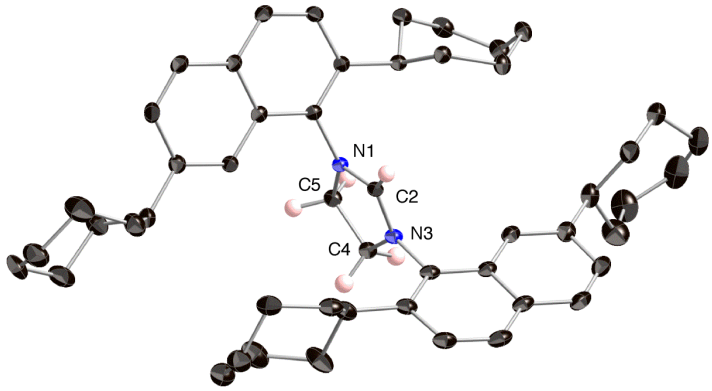


Figure 2. Ellipsoid drawings (30 % probability) of 4c (top), 4f (middle) and 4g (bottom). Hydrogen atoms (except for imidazolinium and backbone hydrogen atoms) and counterion (BF_4^-) were omitted for clarity.

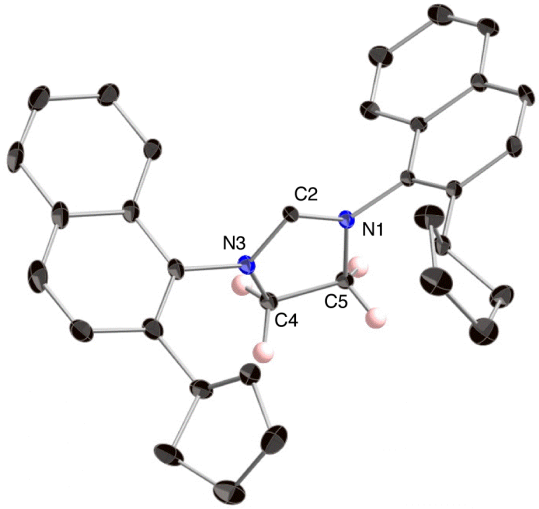


Figure 3. Thermal ellipsoid drawing (30 % probability) of **5b**. Hydrogen atoms (except for backbone hydrogen atoms) were omitted for clarity.

All of the new imidazolinium salts (**4a-h**) and free *N*-heterocyclic carbenes (**5a-h**) were fully characterized and include single crystal X-ray diffraction studies of compounds **4c**, **4f** and **4g** and free carbene **5b**. Thermal ellipsoid drawings of the salts are shown in Figure 2 and a representation of **5b** can be found in Figure 3. Bond lengths and angles of the central five-membered heterocycles of all known imidazolinium salts that incorporate naphthyl side chains are given in Tables 2 and 3.

These tables also include the respective values for **5b**, our previously reported NHCs and the other two known structures in the literature, namely SIMes and SI^{t}Bu.

Table 2. Selected bond lengths of NHC salts with naphthyl wingtips.

Imidazolinium salt	$C_2-N_{1(3)}$	C_4-C_5	$N_{1(3)}-C_{5(4)}$	$N_{1(3)}-C_{Ar}$
syn-(2)-SIMeNap·HBF_4[a]	1.311(3), 1.311(3)	1.522(5)	1.485(3), 1.485(3)	1.440(3), 1.440(3)
anti-(2)-SICyNap·HBF_4[a]	1.313(5), 1.306(5)	1.536(6)	1.479(5), 1.470(5)	1.448(5), 1.448(5)
anti-(2)-SICyheptNap·HBF_4 (**4c**)	1.308(3), 1.315(3)	1.536(3)	1.484(3), 1.479(3)	1.444(3), 1.454(3)
syn-(2,7)-SIPrNap·HCl[a]	1.318(4), 1.307(4)	1.528(4)	1.483(4), 1.481(4)	1.442(4), 1.442(4)
anti-(2,7)-SICyNap·HBF_4 (**4f**)	1.304(3), 1.310(3)	1.542(3)	1.487(2), 1.491(3)	1.440(2), 1.439(3)
anti-(2,7)-SICyheptNap·HBF_4 (**4g**)	1.308(4), 1.301(4)	1.544(4)	1.496(4), 1.490(4)	1.439(4), 1.455(4)
Free carbenes				
syn-(2)-SIPrNap[a]	1.351(2), 1.3498(19)	1.514(2)	1.4814(19), 1.486(2)	1.4266(19), 1.433(2)
syn-(2)-SICypentNap (**5b**)	1.348(2), 1.351(2)	1.520(2)	1.483(2), 1.484(2)	1.423(2), 1.432(2)
syn-(2,7)-SIMeNap[a]	1.344(4), 1.348(4)	1.516(4)	1.480(4), 1.480(4)	1.435(4), 1.433(4)
anti-(2,7)-SIPrNap[a]	1.337(3), 1.354(3)	1.519(4)	1.471(3), 1.473(3)	1.432(4), 1.430(3)
SIMes[b]	1.352(5), 1.345(5)	1.505(6)	1.475(5), 1.487(5)	1.427(5), 1.437(5)
SI^{t}Bu[c]	1.348(1), 1.347(1)	1.512(2)	1.475(1), 1.476(1)	1.480(1), 1.480(1)

[a] For details, see ref. 10. [b] For details, see ref. 4. [c] For details, see ref. 8a.

Table 3. Selected bond angles of NHC salts with naphthyl wingtips and of known free NHCs.

imidazolinium salt	$N_1-C_2-N_3$	$C_{5(4)}-N_{1(3)}-C_2$	$N_{1(3)}-C_{5(4)}-C_{4(5)}$	$C_2-N_{1(3)}-C_{Ar}$
syn-(2)-SIMeNap·HBF_4[a]	113.1(3)	110.5(2), 110.5(2)	102.95(12), 102.95(12)	128.0(2), 128.0(2)
anti-(2)-SICyNap·HBF_4[a]	113.4(4)	110.3(3), 110.6(3)	102.5(3), 102.9(3)	125.2(3), 124.8(3)
anti-(2)-SICyheptNap·HBF_4 (**4c**)	113.58(19)	110.41(17), 110.25(17)	102.63(17), 102.98(17)	127.31(18), 126.28(19)
syn-(2,7)-SIPrNap·HCl[a]	113.5(3)	109.8(2), 109.7(2)	102.1(2), 102.9(2)	124.6(3), 124.8(3)
anti-(2,7)-SICyNap·HBF_4 (**4f**)	114.72(18)	109.98(16), 109.50(17)	102.64(16), 102.73(15)	124.91(16), 123.93(17)
anti-(2,7)-SICyheptNap·HBF_4 (**4g**)	114.8(3)	109.5(2), 110.3(2)	102.8(2), 102.4(2)	124.6(2), 124.0(2)
Free carbenes				
syn-(2)-SIPrNap[a]	104.77(14)	114.52(13), 114.38(13)	101.25(13), 100.94(12)	124.48(14), 122.38(14)
syn-(2)-SICypentNap (**5b**)	105.10(14)	114.64(13), 114.35(14)	101.17(13), 101.29(13)	124.13(13), 122.60(14)
syn-(2,7)-SIMeNap[a]	104.8(2)	115.5(2), 115.3(2)	101.8(2), 101.9(2)	123.6(2), 124.4(2)
anti-(2,7)-SIPrNap[a]	104.5(2)	115.9(2), 115.8(2)	102.3(2), 101.5(2)	125.0(2), 123.9(2)
SIMes[b]	104.7(3)	115.0(3), 114.6(3)	101.6(4), 101.9(4)	122.9(3), 122.5(3)
SI^{t}Bu[c]	106.44(9)	112.51(8), 112.91(8)	101.34(9), 100.96(9)	123.37(9), 123.10(8)

[a] For details, see ref. 10. [b] For details, see ref. 4. [c] For details, see ref. 8a.

The average length of the C_2–$N_{1(3)}$ bonds in these free carbenes increase only very slightly from the average values found in the imidazolinium salts and indicate a partial double bond character of these bonds.

The remaining distances of the five-membered N-heterocycle in both the salts and the free carbenes identify these as single bonds. The most apparent change in bond angles between imidazolinium salts and free carbenes can be found when looking at the N–C–N angles, which are opened in the salts relative to the free carbene species.

3.4 Conclusions

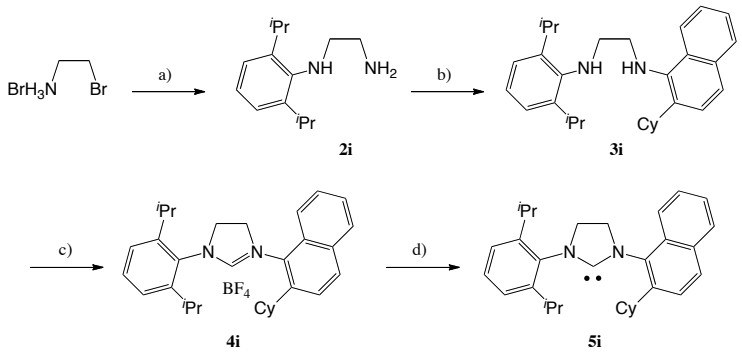
A new, regioselective and scalable procedure for the synthesis of 2,7-disubstituted naphthyl rings was developed and relies on an Iron-catalyzed coupling procedure involving alkylbromides and the corresponding Grignard derivatives of the naphthalene moieties. These units were then selectively brominated at low temperature to give the corresponding 1-bromonaphthalene in quantitative yield. Subsequent Buchwald-Hartwig coupling with ethylene diamine and ring-closing gave eight new imidazolinium salts. Final deprotonation proceeded smoothly and permitted to considerably extend the family of known, stable NHC ligands featuring a saturated central N-heterocyclic backbone. Interestingly, through carefully tuning and enlarging the substituents on positions 2 or 2,7 of the naphthyl side chains, NHC molecules were generated that display a very strong preference to assume only the *anti* conformation. The subtle steric differences of these new structures should allow a more thorough investigation of their behavior when used as organocatalysts or as monodentate ligands in metal complexes and pertinent research on stoichiometric and catalytic activities of these species will be published in due course.

3.5 Supplementary data

All the NHCs presented in this paper were symmetrically substituted in position N,N'. Attempt to synthesize unsymmetric compounds were also successfully performed (Scheme 3). The main idea in this new type of carbene was to avoid the

formation of two diastereoisomers in solution (*syn* and *anti*) by simply exchanging one of the side chains with a properly substituted phenyl ring (moving from a C_2 symmetric molecule to a C_s symmetric one).

Scheme 3. Synthesis of an unsymmetrically substituted free carbene.



Conditions: (a) 2,6 di-isopropylaniline, Toluene, KOH-H_2O, reflux. (b) 1-Bromo-2-cyclohexylnaphthalene, *rac*-BINAP, Pd_2dba_3, ^{t}BuONa. (c) NH_4BF_4, $(EtO)_3CH$, HCOOH cat, 110 °C, 78 %. (d) NaH, ^{t}BuOK cat, THF.

The synthesis of the desired compound started from **2i**, which was synthesized as previously described in literature.[19] The obtained di-amine was then transformed in **3i** via standard C-N Buchwald-Hartwig coupling.

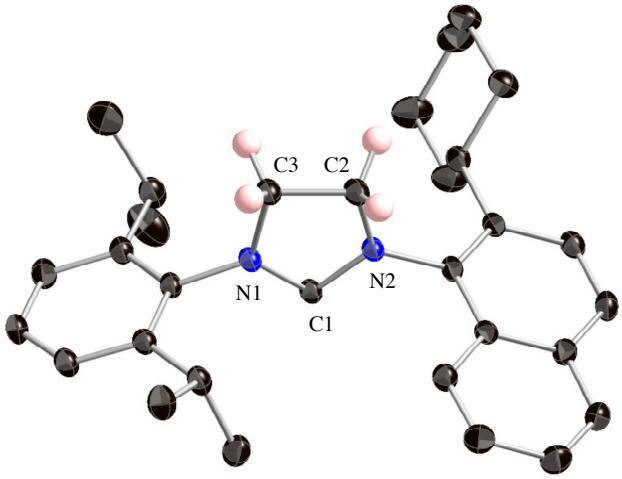


Figure 4. Thermal ellipsoid drawing (30 % probability) of **5i**. Hydrogen atoms (except for backbone hydrogen atoms) were omitted for clarity.

Ring closure and generation of the free carbene **5i** also proceeded in high yield using the same reaction condition employed above. Characterization of the final compound includes crystal X-ray diffraction analysis. Thermal ellipsoid drawings of **5i** can be found in Figure 4.

The high stability displayed from this compound, together with the simple and high yielding synthesis, make **5i** a good candidate for further studies and application in organometallic chemistry.

3.6 Experimental section

General. All reactions were carried out using standard Schlenk or glovebox (Mecaplex or Innovative Technology) techniques under nitrogen atmosphere. All reagents were used as received unless otherwise noted. Solvent were purchased in the best quality available, degassed by purging thoroughly with nitrogen and dried over molecular sieves of appropriate size. Alternatively, they were purged with argon and passed through alumina columns in a solvent purification system (Innovative Technology). Solvent for NMR spectroscopy were degassed with nitrogen and dried over molecular sieves. NMR spectra were measured on an AV2 400 or AV2 500 MHz Bruker spectrometer. Chemical shifts are given in ppm. The spectra are calibrated with respect to the residual ^{1}H and ^{13}C signals of the solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). High-resolution electrospray ionization mass spectrosmetry was performed on a *FinniganMAT 900* (Finnigan MAT95, San Jose, CA; USA) double-focusing magnetic sector mass spectrometer (geometry BE). GC-MS analysis was done on a Finnigan Voyager GC8000 Top. 4-bromo-heptane, bromocyclopentane, bromocycloheptane and bromocyclooctane were purchased from ABCR or Acros and used as reveived.

$(FeCl_3)_2(TMEDA)_3$. A partial modification of the original procedure described by Cahiez et al.[x] was employed. In a glovebox, a one-liter flask was filled with 500 ml of THF and then $FeCl_3$ (9.73 g, 60 mmol) was added slowly as a solid (caution: reaction

is exothermic and the solvent starts to boil). After 10 min, TMEDA (10.46 g, 90 mmol) was added dropwise and the color changed rapidly to brown-red. This mixture was stirred for 1 hour at room temperature; in this period of time only a very small amount of precipitate was formed. The solvent was then completely evaporated and 100 ml of pentane were added. The walls and the bottom of the flask were scratched until an orange suspension was obtained and then it was stirred for 1 hour. The solvent was decanted and the remaining solid was washed other 2 times with 100 ml of pentane. After 12 hours under high vacuum the desired product was obtained as a yellow powder (19.5 g, 95 % yield).

2,7-Dibromonaphthalene. A three-liter 3-neck round-bottomed flask equipped with a mechanistic stirrer was charged with PPh_3 (720.00 g, 2.75 mol) and 1 liter of dry acetonitrile. The mixture was stirred at 70 °C until an homogeneous solution was obtained and then it was cooled to 0°C to form an uniform, fine suspension to which Br_2 (120 ml) was added dropwise in 1 h. 2,7-dihydroxynaphthalene (200.00 g, 1.25 mol) was added solid in portion at room temperature and the mixture was heated at 70°C until an homogeneous solution was formed. At this point the flask was fitted with a distillation head and it was heated until almost all the solvent was distilled. The dark red residue was heated to 270 °C and then maintained at this temperature for 1 h during which time a strong HBr evolution was observed (it was trapped by means of beaker filled with NaOH solution). The dark oil was allowed to cool to 100 °C, poured into EtOH (1 l) and then allowed to sit overnight. The crude product was isolated by filtration and then recrystallized from ethanol. The final gray solid was dried completely and then purified by filtering through siliga gel (hexane as eluent) to get the title product as white solid (148 g, 49 % yield).

<u>General procedure for the iron-catalyzed C-C coupling:</u>

2-(4-heptyl)naphthalene (1a). In a 250 mL 3-necked flask, equipped with condenser, addition funnel and N_2 inlet, were added magnesium (1.18 g, 48.3 mmol) and I_2 (one crystal) under N_2. In the addition funnel were charged 2-bromonaphthalene (10.00 g, 48.30 mmol) and THF (70 ml). A small amount of this solution was added to the flask

and warmed with the heat gun until the color became light brown. The reaction mixture was then heated to 60˚C (oil bath) and the remaining 2-bromonaphthalene solution was added dropwise. At the end of the addition, the mixture was further refluxed for 1h. In the meanwhile, in a 250 ml Schlenk flask containing 60 ml of dry THF where charged 4-bromoheptane (6.66 g, 37.20 mmol) and $(FeCl_3)_2(TMEDA)_3$ (0.75 g, 1.12 mmol). To this flask was then added dropwise the Grignard reagent previously generated; the resulting black mixture was stirred for 30 min at room temperature. The reaction was quenched with aqueous HCl (1 M solution) and extracted with Et_2O (2x150 ml). After evaporation of the solvent, the crude product was heated at 90 °C under high vacuum to eliminate the excess of alkyl bromide and naphthalene. The desired product was isolated after flash chromatography (eluent: hexane) as colorless oil (7.30 g, 92 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (m, 3H), 7.61 (s, 1H), 7.52-7.42 (m, 2H), 7.37 (m, 1H), 2.76 (m, 1H), 1.77-1.64 (m, 4H), 1.30-1.15 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.0, 133.9, 132.5, 128.1, 127.9, 127.8, 126.6, 126.3, 126.0, 125.2, 45.9, 39.4, 21.1, 14.4. HRMS (EI) *m/z* calcd for $C_{17}H_{22}$: 226.1722. Found: 226.1722.

2-cyclopentylnaphthalene (1b). Following the general procedure [2-bromonaphthalene (10.00 g, 48.30 mmol, 60 ml THF), Mg (1.18 g, 48.30 mmol), catalyst (0.75 g, 1.12 mmol), bromocyclopentane (5.54 g, 37.20 mmol, 30 ml THF)], the desired product was obtained after flash chromatography (eluent: hexane) as colorless oil (4.70 g, 64 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (m, 3H), 7.67 (s, 1H), 7.43 (m, 3H), 3.21 (m, 1H), 2.20 (m, 2H), 1.95-1.60 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.3, 133.9, 132.3, 128.1, 127.9, 127.8, 126.4, 126.1, 125.3, 125.1, 46.3, 34.8, 25.9. HRMS (EI) *m/z* calcd for $C_{15}H_{16}$: 196.1252. Found. 196.1255.

2-cycloheptylnaphthalene (1c). Following the general procedure [2-bromonaphthalene (10.00 g, 48.30 mmol, 100 ml THF), Mg (1.18 g, 48.30 mmol), catalyst (0.75 g, 1.12 mmol), bromocycloheptane (6.59 g, 48.30 mmol, 50 ml THF)], the desired product was obtained after flash chromatography (eluent: hexane) as

colorless oil (7.40 g, 89 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (m, 3H), 7.62 (s, 1H), 7.40 (m, 3H), 2.84 (m, 1H), 2.05-1.40 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.7, 134.0, 132.2, 128.1, 127.9, 127.8, 126.4, 126.0, 125.2, 124.6, 47.4, 37.0, 28.3, 27.6. HRMS (EI) *m/z* calcd for $C_{17}H_{20}$: 224.1565. Found: 224.1565.

2-cyclooctylnaphthalene (1d). Following the general procedure [2-bromonaphthalene (15.00 g, 72.40 mmol, 80 ml THF), Mg (1.76 g, 72.40 mmol), catalyst (1.12 g, 1.67 mmol), bromocyclooctane (10.60 g, 55.70 mmol, 40 ml THF)], the desired product was obtained after flash chromatography (eluent: hexane) as white solid (9.50 g, 72 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.75 (m, 3H), 7.60 (s, 1H), 7.39 (m, 3H), 2.92 (m, 1H), 1.95-1.45 (m, 14H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.1, 133.9, 132.2, 128.1, 127.9, 127.7, 126.7, 126.0, 125.2, 124.8, 45.0, 34.8, 27.3, 26.7, 26.3. HRMS (EI): *m/z* : calcd for $C_{18}H_{22}$: 238.1722; Found: 238.1725.

General procedure for the iron-catalyzed double C-C coupling:

2,7-dicyclopentylnapthalene (1e). In a 500 mL 3-necked flask, equipped with condenser, addition funnel and N_2 inlet, were added magnesium (2.40 g, 100.00 mmol) and I_2 (one crystal) under N_2. In the addition funnel were charged 2,7-dibromonaphtalene (13.00 g, 45.40 mmol) and THF (250 ml). A small amount of this solution was added into the flask and warmed with the heat gun until the color became light brown. The reaction mixture was then heated to 60˚C (oil bath) and the remaining solution was added dropwise. At the end of the addition, the mixture was refluxed for another 2 hours. The obtained red-orange suspension was cooled and then cannulated,[20] into a 500 ml schlenk flask containing bromocyclopentane (13.50 g, 90.80 mmol) and $(FeCl_3)_2(TMEDA)_3$ (0.92 g, 1.57 mmol) in dry THF (100 ml). After the addition, the resulting black mixture was stirred for 1 hour at room temperature. The reaction was then quenched with aqueous HCl (1 M solution) and extracted with Et_2O. After evaporation of the solvent, the obtained yellow oil was plugged through a silica gel pad (eluent: hexane) to remove metal contaminants and give a 4:1 mixture of

desired product and mono-substituted alkylnaphthalene. The latter could be eliminated by Kugelrohr distillation (120-125 °C, 0.01 mbar). The desired product was obtained as a white solid (4.19 g, 35 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.59 (s, 2H), 7.33 (d, J = 8.5 Hz, 2H), 3.12 (m, 2H), 2.20-2.00 (m, 4H), 1.81-1.60 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.25, 133.97, 130.89, 127.7, 125.7, 124.7, 46.4, 34.8, 25.9. HRMS (EI) *m/z* calcd for $C_{20}H_{24}$: 264.1878. Found: 264.1880.

2,7-dicyclohexylnapthalene (1f). Following the general procedure [2,7-dibromonaphthalene (30.00 g, 105.00 mmol, 500 ml THF), Mg (5.61 g, 231.00 mmol), catalyst (2.12 g, 3.15 mmol), bromocyclohexane (34.00 g, 210.00 mmol, 200 ml THF)], the desired product was obtained as a white solid (13.70 g, 45 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 7.8 Hz, 2H), 7.54 (s, 2H), 7.28 (d, J = 7.8 Hz, 2H), 2.64 (m, 2H), 2.00-1.82 (m, 10H), 1.61-1.23 (m, 10H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.7, 134.1, 131.0, 127.6, 125.6, 124.4, 44.9, 34.7, 27.2, 26.5. HRMS (EI) *m/z* calcd for $C_{22}H_{26}$: 292.2191. Found: 292.2191.

2,7-dicycloheptylnapthalene (1g). Following the general procedure [2,7-dibromonaphthalene (10.00 g, 35.00 mmol, 400 ml THF), Mg (2.50 g, 102.88 mmol), catalyst (1.20 g, 1.78 mmol), bromocycloheptane (12.40 g, 70.02 mmol, 100 ml THF)], the desired product was obtained as a white solid (3.50 g, 31 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.52 (s, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 2.84 (m, 2H), 2.10-1.50 (m, 24H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.6, 134.1, 130.6, 127.7, 125.5, 124.2, 47.3, 37.0, 28.3, 27.5. HRMS (EI) *m/z* calcd for $C_{24}H_{32}$: 320.2504. Found: 320.2500.

2,7-dicyclooctylnapthalene (1h). Following the general procedure [2,7-dibromonaphthalene (12.00 g, 42.00 mmol, 200 ml THF), Mg (2.55 g, 105.00 mmol), catalyst (0.85 g, 1.26 mmol), bromocyclooctane (16.00 g, 84.00 mmol, 100 ml THF)], the desired product was obtained as a white solid (6.10 g, 42 % yield). ^{1}H NMR

($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.5 Hz, 2H), 7.52 (s, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 2.89 (m, 2H), 1.95-1.50 (m, 28H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.0, 134.1, 130.6, 127.7, 125.8, 124.5, 45.0, 34.8, 27.3, 26.7, 26.3. HRMS (EI) *m/z* calcd for $C_{26}H_{36}$: 348.2817. Found: 348.2813.

General procedure for the bromination of 2- and 2,7-alkyl substituted naphthalene:

1-bromo-2-(4-heptyl)naphthalene (2a). Compound **1a** (5.00 g, 23.55 mmol) was dissolved in 100 ml of dry CH_2Cl_2 in a Schlenk flask and the solution was cooled to -78°C. At this temperature a solution of Br_2 (3.76 g, 23.55 mmol) in CH_2Cl_2 (50 ml) was slowly added. The reaction was left stirring at the same temperature for 5 hours and was subsequently quenched with aqueous NaOH (1M solution, 100 ml). The organic phase was separated, washed with 200 ml of water, dried with $MgSO_4$, filtered and concentrated under vacuum to afford a orange oil. After purification on a silica gel pad (eluent: hexane) to eliminate residual Br_2, the desired product was obtained as a colorless oil (6.80 g, 99 % yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.78 (m, 2H), 7.57 (t, *J* = 8.3 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 3.63 (m, 1H), 1.77-1.51 (m, 4H), 1.34-1.08 (m, 4H), 0.85 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 133.5, 132.8, 128.3, 128.2, 128.0, 127.4, 126.0, 125.3, 125.2, 44.2, 39.1, 20.7, 14.5. HRMS (EI) *m/z* calcd for $C_{17}H_{21}Br$ 304.0827. Found: 304.0830.

1-bromo-2-cyclopentylnaphthalene (2b). Following the general procedure using **1b** (4.20 g, 21.40 mmol, 80 ml CH_2Cl_2) and Br_2 (3.42 g, 21.40 mmol, 80 ml CH_2Cl_2), the desired product was obtained as a nearly colorless oil (5.75 g, 98 % yield). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, *J* = 8.5 Hz, 1H), 7.78 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 3.72 (hept, *J* = 8 Hz, 1H), 2.2 (m, 2H), 1.95-1.60 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 133.5, 132.8, 128.2, 128.0, 127.9, 127.5, 126.0, 125.1, 124.2, 46.0, 34.1, 26.2. HRMS (EI) *m/z* calcd for $C_{15}H_{15}Br$: 274.0357. Found: 274.0352.

1-bromo-2-cycloheptylnaphthalene (2c). Following the general procedure using **1c** (5.70 g, 25.60 mmol, 50 ml CH_2Cl_2) and Br_2 (4.09 g, 25.29 mmol, 80 ml CH_2Cl_2), the

desired product was obtained as a colorless oil (7.60 g, 99 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.36 (d, *J* = 8.5 Hz, 1H), 7.78 (m, 2H), 7.58 (m, 1H), 7.48 (m, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 3.52 (m, 1H), 2.05-1.50 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.5, 133.3, 132.7, 128.2, 128.1, 128.0, 127.4, 125.9, 125.5, 122.8, 46.2, 35.8, 28.2, 27.9. HRMS (EI) *m/z* calcd for $C_{17}H_{19}Br$: 302.0673. Found: 302.0673.

1-bromo-2-cyclooctylnaphthalene (2d). Following the general procedure using **1d** (5.00 g, 21.00 mmol, 80 ml CH_2Cl_2) and Br_2 (3.35 g, 21.00 mmol, 80 ml CH_2Cl_2), the desired product was obtained as a transparent oil (6.65 g, 99 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (d, *J* = 8.4 Hz 2H), 7.75 (m, 1H), 7.55 (m, 1H), 7.44 (m, 1H), 7.37 (d, *J* = 8.4 Hz 3H), 3.68 (m, 1H), 1.90-1.52 (m, 14H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.33, 133.31, 132.75, 128.17, 128.09, 128.08, 127.44, 125.94, 122.87, 43.58, 34.56, 27.18, 26.88, 26.59. HRMS (EI): *m/z* : calcd for $C_{18}H_{21}Br$: 316.0827. Found: 316.0823.

1-bromo-2,7-dicyclopentylnaphthalene (2e). Following the general procedure using **1e** (2.13 g, 8.06 mmol, 20 ml CH_2Cl_2) and Br_2 (1.29 g, 8.06 mmol, 20 ml CH_2Cl_2), the desired product was obtained as a colorless oil (2.70 g, 98 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.34 (m, 2H), 3.80 (m, 1H), 3.20 (m, 1H), 2.20-1.5 (m, 16H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.0, 143.6, 132.8, 132.1, 128.2, 127.7, 126.2, 125.2, 124.3, 123.9, 46.7, 46.0, 35.0, 34.1, 26.2, 26.0. HRMS (EI) *m/z* calcd for $C_{22}H_{27}Br$: 342.0983. Found: 342.0980.

1-bromo-2,7-dicyclohexylnaphthalene (2f). Following the general procedure using **1f** (2.20 g, 7.52 mmol, 60 ml CH_2Cl_2) and Br_2 (1.26 g, 7.90 mmol, 20 ml CH_2Cl_2), the desired product was obtained as a light yellow oil (2.75 g, 98 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (s, 1H), 7.68 (m, 2H), 7.34 (m, 2H), 3.35 (m, 1H), 2.71 (m, 1H), 2.00-1.2 (m, 20H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.4, 144.3, 132.8, 132.1, 128.1, 127.6, 126.1, 124.9, 124.3, 123.5, 45.3, 44.7, 34.7, 33.4, 27.2, 27.1, 26.5, 26.4. HRMS (EI) *m/z* calcd for $C_{22}H_{27}Br$: 370.1296. Found: 370.1297.

1-bromo-2,7-dicycloheptylnaphthalene (2g). Following the general procedure using **1g** (1.20g, 3.74 mmol, 40 ml CH_2Cl_2) and Br_2 (0.59 g, 3.70 mmol, 40 ml CH_2Cl_2), the desired product was obtained as light yellow oil (1.50 g, 99 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 1H), 7.68 (m, 2H), 7.34 (m, 2H), 3.51 (m, 1H), 2.85 (m, 1H), 2.08-1.5 (m, 24H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.1, 147.0, 132.9, 132.0, 128.3, 127.8, 126.0, 124.7, 122.9, 47.7, 37.1, 35.9, 28.3, 28,2 27.9, 27.6. HRMS (EI) *m/z* calcd for $C_{24}H_{31}Br$: 398.1609. Found: 398.1610.

1-bromo-2,7-dicyclooctylnaphthalene (2h). Following the general procedure using **1h** (9.40 g, 27.00 mmol, 300 ml CH_2Cl_2) and Br_2 (4.31 g, 27.00 mmol, 200 ml CH_2Cl_2), the desired product was obtained as colorless oil (11.40 g, 99 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.32 (m, 2H), 3.71 (m, 1H), 2.98 (m, 1H), 2.00-1.5 (m, 28H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 149.8, 147.2, 132.8, 131.8, 128.3, 127.7, 126.3, 125.0, 124.9, 122.7, 45.4, 35.0, 34.6, 27.2, 27.1, 26.9, 26.7, 26.6 HRMS (EI) *m/z* calcd for $C_{26}H_{35}Br$: 426.1922. Found: 426.1916.

General procedure for the C-N Buchwald-Hartwig coupling:

N,N'-Bis(2-(4-heptyl)naphthalene-1yl)ethane-1,2-diamine (3a). In a glove box, a Schlenk flask was charged with *rac*-BINAP (0.27 g, 0.42 mmol), $Pd(dba)_2$ (0.23 g, 0.387 mmol) NaO^tBu (1.15 g, 11.60 mmol) and toluene (50 ml). The resulting violet suspension was stirred at room temperature for 10 minutes and then **2a** (2.60 g, 8.52 mmol) was added. After another 5 minutes ethylenediamine (0.23 g, 3.87 mmol) was added, the flask was taken out of the glovebox, connected to a condenser and the suspension was refluxed for 18 hours. The mixture was cooled to room temperature and then passed through a celite filter to eliminate the inorganic salts. After evaporation of the solvent the obtained oil was purified by silica gel chromatography (eluent: hexane-CH_2Cl_2 3:1) to yield the desired product as yellow oil (1.25 g, 63 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.6 Hz, 2H), 7.48-7.38 (m, 4H), 7.33 (d, *J* = 8.3 Hz, 2H), 4.05-3.85 (s, broad, 2H), 3.43 (s, 4 H), 3.18 (m, 2H), 1.75-1.55 (m, 10H), 1.32-1.12 (m, 12H),

0.85 (t, J = 7.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.0, 133.2, 129.7, 128.4, 125.8, 125.3, 124.9, 124.2, 123.9, 52.0, 39.5, 34.9, 31.8, 27.1, 25.5, 22.9, 21.4, 14.6. HRMS (ESI) m/z calcd for $C_{30}H_{48}N_2$: 508.3896. Found: 509.3893 [M+1].

N,N'-Bis(2-cyclopentylnaphthalene-1yl)ethane-1,2-diamine (3b). Following the general procedure [*rac*-BINAP (0.41 g, 0.65 mmol), $Pd(dba)_2$ (0.31 g, 0.54 mmol), NaO^{t}Bu (1.57 g, 16.40 mmol), Toluene (140 ml), **2b** (3.00 g, 10.90 mmol), ethylenediamine (0.32 g, 5.34 mmol)], the desired product was obtained after silica gel chromatography (eluent: hexane-EtOAc 10:1) as a yellow oil (2.20 g, 92 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 7.9 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.52-7.39 (m, 6H), 3.95 (s, 2H), 3.55 (m, 2H), 3.45 (s, 4H), 2.12 (m, 4H), 2.00-1.70 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.0, 135.2, 133.4, 129.5, 128.5, 125.9, 125.3, 125.2, 124.0, 123.4, 52.3, 40.1, 35.1, 26.4. HRMS (ESI) m/z calcd for $C_{32}H_{36}N_2$: 448.2878. Found: 449.2945 [M+1].

N,N'-Bis(2-cycloheptylnaphthalene-1yl)ethane-1,2-diamine (3c). Following the general procedure [*rac*-BINAP (0.12 g, 0.19 mmol), $Pd(dba)_2$ (0.095 g, 0.16 mmol), NaO^{t}Bu (0.48 g, 5.00 mmol), Toluene (50 ml), **2c** (1.00 g, 3.30 mmol), ethylenediamine (0.097 g, 1.62 mmol)], the desired product was obtained after silica gel chromatography (eluent: hexane-EtOAc 10:1) as a yellow foam (0.71 g, 87 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, J = 8.5 Hz, 2H), 7.81 (d, J = 7.9 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.52-7.39 (m, 6H), 3.90 (s, 2H), 3.45 (s, 4H), 3.35 (m, 2H), 2.00-1.50 (m, 24H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.2, 139.1, 133.3, 129.8, 128.5, 125.9, 125.7, 125.2, 124.2, 123.6, 52.4, 40.7, 36.9, 28.2, 28.1. HRMS (EI) m/z calcd for $C_{36}H_{44}N_2$: 504.3504. Found: 504.3511.

N,N'-Bis(2-cyclooctylnaphthalene-1yl)ethane-1,2-diamine (3d). Following the general procedure [*rac*-BINAP (0.34 g, 0.55 mmol), $Pd(dba)_2$ (0.26 g, 0.45 mmol), NaO^{t}Bu (1.31 g, 13.60 mmol), Toluene (100 ml), **2d** (3.17 g, 10.0 mmol), ethylenediamine (0.27 g, 4.55 mmol)], the desired product was obtained after silica gel chromatography (eluent: hexane-EtOAc 10:1) as an off-white powder (1.60 g, 66

% yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (s, broad, 2H), 7.78 (d, *J* = 8 Hz, 1H), 7.58 (d, *J* = 8.9 Hz, 2H), 7.48-7.33 (m, 6H), 4.20-3.50 (s, broad, 2H), 3.52 (m, 6H), 1.90-1.42 (m, 14H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.15, 140.02, 133.25, 129.84, 128.49, 126.09, 125.92, 125.25, 124.25, 123.67, 52.40, 38.04, 35.62, 27.04, 26.93, 26.87. HRMS (ESI) *m/z* calcd for $C_{38}H_{48}N_2$: 532.3895. Found: 533.3890 [M+1].

N,N'-Bis(2,7-dicyclopentylnaphthalene-1yl)ethane-1,2-diamine (3e). Following the general procedure [*rac*-BINAP (0.41 g, 0.65 mmol), $Pd(dba)_2$ (0.31 g, 0.54 mmol), NaO^{t}Bu (1.57 g, 16.44 mmol), Toluene (140 ml), **2e** (3.00 g, 10.91 mmol), ethylenediamine (0.32 g, 5.34 mmol)], the desired product was obtained after silica gel chromatography (eluent: hexane-EtOAc 20:1 to 10:1) as a yellow oil (2.20 g, 92 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.10 (s, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.6 Hz 2H), 7.33 (d, J = 8.5 Hz, 4 H), 3.90 (s, broad 2H), 3.50 (m, 2H), 3.42 (s, 4H), 3.13 (m, 2H), 2.15-1.60 (m, 32H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 141.7, 135.1, 132.0, 129.4, 128.4, 125.6, 124.3, 123.6, 120.7, 52.1, 46.7, 40.1, 35.1, 35.0, 26.3, 25.9. HRMS (EI) *m/z* calcd for $C_{42}H_{52}N_2$: 584.4130. Found: 585.4207 [M+1].

N,N'-Bis(2,7-dicyclohexylnaphthalene-1yl)ethane-1,2-diamine (3f). Following the general procedure [*rac*-BINAP (0.24 g, 0.39 mmol), $Pd(dba)_2$ (0.20 g, 0.35 mmol), NaO^{t}Bu (0.99 g, 10.32 mmol), Toluene (50 ml), **2f** (2.90 g, 7.81 mmol), ethylenediamine (0.21 g, 3.55 mmol)], the desired product was obtained after silica gel chromatography (eluent: hexane-CH_2Cl_2 3:1 to 2:1) as a crystalline white solid (2.00 g, 88 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.5 Hz 2H), 7.33 (m, 4 H), 3.90 (s, broad 2H), 3.42 (s, 4H), 3.12 (m, 2H), 2.63 (m, 2H), 1.95-1.10 (m, 40H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.6, 141.0, 136.7, 132.0, 129.7, 128.3, 125.5, 124.4, 123.6, 120.4, 52.2, 45.3, 39.1, 34.8, 34.5, 27.4, 27.1, 26.5, 26.4. HRMS (EI) *m/z* calcd for $C_{46}H_{60}N_2$: 640.4756. Found: 641.4825 [M+1].

N,N'-Bis(2,7-dicycloheptylnaphthalene-1yl)ethane-1,2-diamine (3g). Following the general procedure [*rac*-BINAP (0.25 g, 0.40 mmol), $Pd(dba)_2$ (0.17 g, 0.30

mmol), NaO^{t}Bu (1.07 g, 11.10 mmol), Toluene (150 ml), **2g** (2.90 g, 7.26 mmol), ethylenediamine (0.21 g, 3.46 mmol)], the desired product was obtained after silica gel chromatography (eluent: Hexane to Hexane-CH_2Cl_2 1:1) as a crystalline white solid (2.11 g, 88 %). ^{1}H NMR (Acetone d_6[21], 400 MHz): δ 8.17 (s, 2H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.5 Hz 2H), 7.33 (m, 4 H), 3.76 (s, 4H), 3.45 (m, 2H), 2.69 (m, 2H), 2.20-1.40 (m, 48H). ^{13}C NMR (Acetone d_6, 100 MHz): δ 147.1, 140.6, 139.1, 132.2, 130.3, 128.5, 125.3, 124.8, 123.6, 120.8, 68.9, 68.8, 52.1, 47.8, 40.3, 37.2, 37.0, 28.2, 28.1, 27.4. HRMS (EI) *m/z* calcd for $C_{50}H_{68}N_2$: 696.5382. Found: 697.5455 [M+1].

N,N'-Bis(2,7-dicyclooctylnaphthalene-1yl)ethane-1,2-diamine (3h). Following the general procedure [*rac*-BINAP (0.44 g, 0.70 mmol), $Pd(dba)_2$ (0.34 g, 0.58 mmol), NaO^{t}Bu (1.69 g, 17.64 mmol), Toluene (150 ml), **2b** (5.00 g, 15.72 mmol), ethylenediamine (0.34 g, 5.70 mmol)], the desired product was obtained after silica gel chromatography (eluent: Hexane-EtOAc 15:1 to 10:1) as a yellow solid (3.50 g, 81 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.08 (s, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.5 Hz 2H), 7.38 (m, 4 H), 3.92 (s, broad 2H), 3.45 (s, 6H), 2.89 (m, 2H), 1.95-1.10 (m, 56H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 147.8, 139.9, 139.8, 131.7, 129.9, 128.4, 125.8, 125.1, 123.8, 120.5, 52.3, 45.5, 38.0, 35.6, 34.7, 27.3, 27.0, 26.9, 26.8, 26.4, 26.3. HRMS (EI) *m/z* calcd for $C_{54}H_{76}N_2$: 752.6008. Found: 752.6005.

Synthesis of imidazolinium salts:

1,3-Bis(2-(4-heptyl)naphthalen-1-yl)-imidazolinium tetrafluoroborate (4a). To a Schlenk tube containing **3a** (1.10 g, 2.16 mmol) and NH_4BF_4 (0.36 g, 3.46 mmol), was added $(EtO)_3CH$ (20 ml). To this suspension was added formic acid (3 drops) and the mixture was heated at 110˚C for 2 hours. After this time a small amount of white solid was present in the suspension. The solvent was distilled out and the obtained brown foam was purified by silica gel chromatography (eluent: Hexane to CH_2Cl_2 to CH_2Cl_2-MeOH 40:1). To the obtained light yellow oil were added ether (3 ml) and pentane (10 ml) to induce the precipitation of a white powder that, from NMR analysis, proved to be the desired compound (1.31 g, 75 % yield). From NMR

analysis a 43:57 mixture of two isomers was detected. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.7 Hz, 2H), 7.97-7.84 (m, 4H), 7.78-760 (m, 4H), 7.52 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 5.30-4.65 (m, 4H), 3.22-2.97 (m, 2H), 2.05-140 (m, 10H), 1.30-0.70 (m, 18H). (Due to the existence of two atropisomers, ^{13}C NMR spectrum appeared complex) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.8, 159.5, 143.0, 142.1, 133.03, 133.02, 132.2, 132.1, 130.0, 129.7, 129.5, 129.4, 129.1, 128.9, 128.2, 128.0, 127.6, 127.4, 124.4, 123.9, 121.3, 120.6, 54.8, 54.7, 41.23, 41.21, 39.8, 39.1, 39.0, 38.5, 22.0, 21.7, 21.6, 21.5, 14.7, 14.62, 14.60, 14.5. ^{19}F NMR ($CDCl_3$, 376 MHz): δ -148.34, -148.31. HRMS (ESI) *m/z* calcd for $C_{37}H_{47}BF_4N_2$: 606.3768. Found: 519.3798 [M-BF_4].

1,3-Bis(2-cyclopentylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (4b). To a Schlenk tube under nitrogen containing **3b** (2.20 g, 4.90 mmol) and NH_4BF_4 (0.64 g, 5.88 mmol), were added $(EtO)_3CH$ (20 ml) and formic acid (3 drops). The mixture was then heated at 110˚C for 5 hours. After this the resulting suspension was cooled to room temperature and filtered to eliminate most of the $(EtO)_3CH$. The obtained yellow solid was dissolved in CH_2Cl_2 and filtered through celite to eliminate the excess of NH_4BF_4. The filtrate was concentrated under vacuum until a yellow oil was obtained. Toluene (70 ml) was then added and the obtained mixture was sonicated for 15 minutes at room temperature and then heated at 75°C until a homogeneous yellow suspension was formed. It was cooled to ca. 50°C and filtered. The obtained solid was washed with 10 ml of Et_2O and dried under high vacuum overnight (1.75 g, 65 % yield). From NMR analysis a 50:50 mixture of *syn-anti* isomer was observed. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.58 – 9.52 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.7 Hz, 2H), 8.1 (m, 3H), 7.83 (m, 1H), 7.78 (m, 1H), 7.70 (m, 4H), 4.95-4.65 (m, 4H), 3.60 (m, 1H), 3.40 (m, 1H), 2.28 (m, 2H), 2.10-1.50 (m, 16H). (Due to the existence of two atropisomers, ^{13}C NMR spectrum appeared complex) ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.6, 161.4, 142.3, 142.2, 132.4, 132.3, 131.1, 131.0, 129.3, 129.1, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 126.8, 125.1, 125.0, 122.0, 121.4, 53.7, 53.6, 40.1 (overlapped with solvent, determined by 2D-HSQC), 39.7 (overlapped with solvent, determined by 2D-HSQC), 36.0, 35.5, 34.7, 33.8, 26.1,

25.9, 25.8, 25.7. ^{19}F NMR (DMSO-d_6, 376 MHz): -148.30, -148.35. HRMS (ESI) *m/z* calcd for $C_{33}H_{35}BF_4N_2$: 546.2829. Found: 459.2795 [M-BF_4].

1,3-Bis(2-cycloheptylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (4c). To a Schlenk tube under nitrogen containing **3c** (0.71 g, 1.41 mmol) and NH_4BF_4 (0.16 g, 1.55 mmol), were added $(EtO)_3CH$ (7 ml) and formic acid (2 drops). The mixture was then heated at 120˚C for 3 hours. The resulting suspension was cooled to room temperature and filtered to eliminate most of the $(EtO)_3CH$. The obtained yellow solid was dissolved in CH_2Cl_2 and filtered through celite to eliminate the excess of NH_4BF_4. The solution was then concentrated under vacuum and, upon addition of Et_2O, a white powder precipitated. The solvent was decanted and the solid was washed with cold Et_2O (2 × 20 ml) and with cold CH_2Cl_2 (1 × 10 ml). The desired product was dried under high vacuum for 12 hours (0.49 g, 58 % yield). From NMR analysis 22 % of the *syn* isomer was detected. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.68 – 9.56 (s, 1H), 8.23 -8.04 (m, 6H), 7.88 – 7.68 (m, 6H), 7.87 (s, 2H), 5.05-4.65 (m, 4H), 3.10-3.00 (m, 2H), 2.10-1.50 (m, 24H). (Due to the existence of two atropisomers, ^{13}C NMR spectrum appeared complex) ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.6, 162.0, 145.7, 145.3, 132.8, 132.7, 131.7, 131.6, 129.6, 129.5, 129.2, 129.1, 128.7, 127.3, 127.2, 126.8, 126.5, 125.9, 125.8, 122.2, 122.0, 54.3, 54.1, 41.8, 41.1, 36.6, 36.2, 35.9, 35.6, 28.2, 29.0, 27.9, 27.7, 27.6, 27.4, 27.3. ^{19}F NMR (DMSO-d_6, 376 MHz): -148.28, -148.33. HRMS (ESI) *m/z* calcd for $C_{37}H_{43}BF_4N_2$: 602.3455. Found: 515.3418 [M-BF_4].

1,3-Bis(2-cyclooctylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (4d). To a Schlenk tube under nitrogen containing **3d** (1.50 g, 2.81 mmol) and NH_4BF_4 (0.36 g, 3.38 mmol), were added $(EtO)_3CH$ (30 ml) and formic acid (3 drops). The mixture was heated at 100˚C for 2 hours. The suspension was then cooled to room temperature and filtered to eliminate most of the $(EtO)_3CH$. The obtained solid was washed with 30 ml of Et_2O, then dissolved in CH_2Cl_2 (200 ml) and slowly filtered through celite. The solvent was then reduced to ~ 5 ml and Et_2O (60 ml) was added inducing the precipitation of a white powder. The solid was isolated by decantation and dried under high vacuum (1.53 g, 86 % yield). From NMR analysis, two isomers are

present in a 83:17 (*anti-syn*) ratio. Due to overlap of most of the signals of the respective isomers only the ones related to the major isomer will be presented. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.64 (s, 1H), 8.18 (d, J = 8.8 Hz, 2H), 8.12 (d, J = 7.6 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 7.80-7.67 (m, 6H), 5.75 (s, 4H), 5.10-4.65 (m, 4H), 3.20 (m, 2H), 2.15-1.50 (m, 28H). (Due to the existence of two atropisomers, ^{13}C NMR spectrum appeared complex) ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.45, 161.43, 146.06, 145.04, 132.30, 132.20, 131.21, 129.08, 128.98, 128.72, 128.61, 128.20, 126.82, 126.70, 126.28, 125.75, 125.65, 125.58, 121.54, 121.26, 53.80, 53.63, 34.82, 34.15, 33.16, 27.09, 26.86, 26.15, 26.11, 26.02, 25.92, 25.69, 25.45, 25.28, 25.14. ^{19}F NMR (DMSO-d_6, 376 MHz): -143.51, -143.56. HRMS (ESI) *m/z* calcd for $C_{39}H_{47}BF_4N_2$: 630.3768. Found: 543.3727 [M-BF_4].

1,3-Bis(2,7-dicyclopentylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (4e). To a Schlenk tube under nitrogen, containing **3e** (1.60 g, 2.74 mmol) and NH_4BF_4 (0.45 g, 4.10 mmol), were added $(EtO)_3CH$ (30 ml) and formic acid (2 drops). The mixture was then heated at 110˚C for 4 hour. After this it was cooled to room temperature and filtered to eliminate most of the $(EtO)_3CH$. The obtained yellow solid was dissolved in CH_2Cl_2 and filtered through celite to eliminate the excess of NH_4BF_4. The solution was then concentrated in vacuum and, upon addition of Et_2O, a white powder precipitate. The solvent was decanted and the solid was washed with Et_2O (3 × 10 ml). The desired product was then dried in high vacuum for 12 h (0.73 g, 39 % yield). Crystals suitable for X-Ray analysis were obtained through slow evaporation of a toluene-CH_2Cl_2 solution of the product. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.49 (s 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.87 (s, 2H), 7.65 (m, 4H), 5.10-4.60 (m, 4H), 2.90 (m, 4H), 2.10-1.10 (m, 32H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.9, 148.1, 143.0, 131.1, 130.5, 129.2, 128.7, 126.9, 126.0, 124.2, 118.8, 64.9, 53.6, 44.8, 33.9, 33.6, 33.4, 33.1, 26.4, 26.3, 26.2, 25.5, 25.4, 15.1. ^{19}F NMR (DMSO-d_6, 376 MHz): -143.53, -143.58. HRMS (ESI) *m/z* calcd for $C_{43}H_{51}BF_4N_2$: 682.4081. Found: 595.4047 [M-BF_4].

1,3-Bis(2,7-dicyclohexylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (4f). To a Schlenk tube containing **3f** (0.96 g, 1.50 mmol) and NH_4BF_4 (0.19 g, 1.80

mmol), were added $(EtO)_3CH$ (20 ml) and formic acid (3 drops). The mixture was then heated at 110˚C for 1 hour. After this the suspension was cooled to room temperature and filtered to eliminate most of the $(EtO)_3CH$. The obtained yellow solid was dissolved in CH_2Cl_2 and filtered through celite to eliminate the excess of NH_4BF_4. The solution was then concentrated under vacuum and, upon addition of Et_2O, a white powder precipitated. The solvent was decanted and the solid was washed with Et_2O (3 × 10 ml). The desired product was then dried under high vacuum for 12 hours (0.55 g, 50 % yield). Crystals suitable for X-Ray analysis were obtained through slow evaporation of a Toluene/CH_2Cl_2 solution of the product. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.49 (s 1H), 8.13 (d, *J* = 8.7 Hz, 2H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.87 (s, 2H), 7.65 (m, 4H), 5.10-4.60 (m, 4H), 2.90 (m, 4H), 2.10-1.10 (m, 40H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.9, 148.1, 143.0, 131.1, 130.5, 129.2, 128.7, 126.9, 126.0, 124.2, 118.8, 64.9, 53.6, 44.8, 33.9, 33.6, 33.4, 33.1, 26.4, 26.3, 26.2, 25.5, 25.4, 15.1. ^{19}F NMR (DMSO-d_6, 376 MHz): -143.53, -143-58. HRMS (ESI) *m*/*z* calcd for $C_{47}H_{59}BF_4N_2$: 738.4707. Found: 651.4668 [M-BF_4].

1,3-Bis(2,7-dicycloheptylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (4g). Following the same procedure used to synthesize compound **4a** [**3g** (1.04 g, 1.50 mmol), NH_4BF_4 (0.19 g, 1.80 mmol), formic acid (cat.), $(EtO)_3CH$ (25 ml)], the desired product was obtained after silica gel chromatography (CH_2Cl_2 to CH_2Cl_2-MeOH 30:1 as eluent) as a white solid (0.57 g, 48 % yield). From NMR analysis 10 % of the *syn* isomer was detected. Crystals suitable for X-Ray analysis were obtained by heating a suspension of the product in toluene-CH_2Cl_2 until complete dissolution and slowly cooling the sample to room temperature. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.71 (s, 1H), 7.62 (s, 2H), 7.54 (m, 2H), 7.45 (d, *J* = 8.2 Hz, 2H), 5.22-4.71 (m, 4H), 2.98 (m, 4H), 2.10-1.40 (m, 48H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 158.3, 151.6, 145.0, 131.8, 131.5, 129.6, 129.5, 126.6, 125.4, 124.1, 117.8, 54.7, 48.4, 42.6, 37.8, 37.2, 37.1, 37.0, 36.7, 28.5, 28.3, 28.1, 28.0, 27.4, 27.3. ^{19}F NMR (DMSO-d_6, 376 MHz): δ -143.49, -143.54. HRMS (EI) *m*/*z* calcd for $C_{51}H_{67}BF_4N_2$: 707.5304. Found: 707.5305.

1,3-Bis(2,7-dicyclooctylnaphthalen-1-yl)-imidazolinium tetrafluoroborate (4h). To a Schlenk tube containing **3h** (0.41 g, 0.54 mmol) and NH_4BF_4 (0.006 g, 0.60 mmol), were added $(EtO)_3CH$ (6 ml) and formic acid (2 drops). The mixture was then heated to 110˚C for 4 hours and to 90˚C overnight. The suspension was cooled to room temperature and filtered to eliminate most of the $(EtO)_3CH$. The obtained yellow solid was dissolved in CH_2Cl_2 and filtered through celite to eliminate the excess of NH_4BF_4. The solution was then concentrated under vacuum and, upon addition of Et_2O, a white solid precipitated. The solution was decanted and the solid was washed with Et_2O (3 × 10 ml). The desired product was then dried under high vacuum for 12 hours (0.13 g, 29 % yield). From ^{1}H-NMR analysis the two isomers were present in a ratio of 9:1 (*anti*/*syn*). Due to overlap of most of the signals of the two isomers only the ones related to the major isomer are reported. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.99 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.7 Hz, 2H), 7.76 (s, 1H), 7.64 (s, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 5.22-4.75 (m, 4H), 3.10 (s, 4H), 2.20-1.50 (m, 56H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 158.4, 152.3, 145.0, 131.6, 131.5, 129.8, 129.4, 127.1, 125.8, 124.6, 118.0, 54.8, 46.7, 41.7, 35.4, 35.0, 34.2, 33.9, 28.2, 27.7, 27.5, 27.0, 26.4, 26.3, 26.1, 25.9, 24.7. ^{19}F NMR (DMSO-d_6, 376 MHz): -152.63, -152.69. HRMS (ESI) *m*/*z* calcd for $C_{55}H_{75}BF_4N_2$: 850.5959. Found: 763.5917 [M-BF_4].

General procedure for the synthesis of free carbenes:

1,3-Bis(2-(4-heptyl)naphthalen-1-yl)-imidazolin-2-ylidene (5a). To a suspension of **4a** (0.50 g, 0.82 mmol) in dry THF (50 ml) under nitrogen, NaH (55 to 65 % suspension in mineral oil, 0.043 g, 1.07 mmol) and a catalytic amount of KO^{t}Bu were added. The resulting mixture was stirred at room temperature for 15 h. It was then slowly filtered through celite to eliminate the inorganic salts. After evaporation of the solvent, the desired product was obtained as a slightly orange solid (0.42 g, 99 % yield). From NMR analysis two distinct isomers were present in a ratio of approximately 55:45. ^{1}H NMR (C_6D_6, 400 MHz): δ 8.38-8.26 (m, 2H), 7.75-7.64 (m, 4H), 7.57-7.44 (m, 2H), 7.43-7.27 (m, 4H), 3.85-3.51 (m, 6H), 1.91-1.13 (m, 16H), 1.05- 0.73 (m, 12H). ^{13}C NMR (C_6D_6, 100 MHz): δ 247.2, 247.1, 142.5, 142.2, 138.6,

138.5, 134.1, 133.0, 132.7, 129.0, 128.9, 127.2, 126.9, 126.1, 126.0, 125.4, 125.3, 124.6, 124.5, 53.4, 54.2, 40.2, 40.0, 39.9, 39.8, 39.7 38.9, 22.4, 22.3, 21.7, 21.6, 15.4, 15.2, 15.1.

1,3-Bis(2-cyclopentylnaphthalen-1-yl)-imidazolin-2-ylidene (5b). Following the general procedure [**4b** (0.18 g, 0.27 mmol), NaH (0.013 g, 0.33 mmol), KO^{t}Bu (cat.), THF (40 ml)], the desired compound was obtained as an off-white solid (0.11 g, 90 % yield). From NMR analysis two isomers in a 50:50 ratio can be identified. Crystals suitable for X-Ray analysis were obtained through slow diffusion of pentane into a concentrated solution of the product in benzene. ^{1}H NMR (C_6D_6, 500 MHz): δ 8.32 (d, *J* = 8.3 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.68 (m, 4H), 7.52-7.42 (m, 2H), 7.40-7.28 (m, 4H), 3.85-3.40 (m, 6H), 2.35 (m, 2H), 2.17-2.00 (m, 2H), 1.95-1.5 (m, 12H). ^{13}C NMR (C_6D_6, 125 MHz): δ 246.4, 246.2, 142.2, 142.1, 138.2, 138.1, 134.0, 132.7, 132.6, 128.9, 128.8, 128.7, 128.5, 127.3, 127.0, 126.0, 125.9, 125.7, 125.6, 124.4, 124.0, 54.1, 54.0, 41.7, 41.3, 36.3, 36.1, 35.7, 35.2, 27.4, 27.0, 26.9, 26.7.

1,3-Bis(2-cycloheptylnaphthalen-1-yl)-imidazolin-2-ylidene (5c). Following the general procedure starting [**4c** (0.10 g, 0.17 mmol), NaH (0.008 g, 0.20 mmol), KO^{t}Bu (cat.), THF (50 ml)], the desired compound was obtained as an off-white solid (0.09 g, 99 % yield). From NMR analysis 16 % of the *syn* isomer can be identified (due to strong overlap between most of the signals of the two isomers only the ones related to the major isomer are reported). ^{1}H NMR (C_6D_6, 400 MHz): δ 8.30 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.67 (d, *J* = 8.5 Hz, 2H), 7.58 (t, J = 7.5 Hz, 2H), 7.50-7.30 (m, 4H), 3.75-3.42 (m, 4H), 2.25 (m, 2H), 2.00-1.50 (m, 24H). ^{13}C NMR (C_6D_6, 100 MHz): δ 245.7, 145.8, 136.3, 133.9, 132.7, 128.9, 128.7, 126.9, 126.1, 125.9, 124.4, 54.1, 41.5, 38.0, 37.2, 36.8, 29.3, 29.0, 28.4, 28.3.

1,3-Bis(2-cyclooctylnaphthalen-1-yl)-imidazolin-2-ylidene (5d). In a glove box, to a suspension of **4d** (0.40 g, 0.63 mmol) in THF (50 ml), NaH (55 to 65 % suspension in mineral oil, 0.029 g, 0.76 mmol) and a catalytic amount of KO^{t}Bu were added. The obtained mixture was heated to reflux with a heat gun for a few minutes to initiate the reaction and then reaction was stirred at room temperature for 3 h. It was then slowly

filtered through celite to eliminate the inorganic salts. After evaporation of the solvent, 5 ml of Et_2O were added to the sticky pink solid and the resulting suspension was stirred for 5 minutes. The solvent was decanted and the pink solid was dried in high vacuum (0.31 g, 90 % yield). From NMR analysis 17 % of the *syn* isomer was detected. (Due to overlap of most of the signals for both isomers, only the ones related to the major isomer are reported). ^{1}H NMR (C_6D_6, 400 MHz): δ 8.32 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.59 (m, 2H), 7.37 (m, 2H), 3.80-3.40 (m, 6H), 2.22-1.4 (m, 28H). ^{13}C NMR (C_6D_6, 100 MHz): δ 245.8, 146.7, 136.1, 133.9, 132.6, 128.9, 126.9, 126.7, 125.9, 124.6, 54.2, 38.6, 36.4, 36.1, 28.3, 28.1, 27.1, 26.5.

1,3-Bis(2,7-cyclopentylnaphthalen-1-yl)-imidazolin-2-ylidene (5e). Following the general procedure [**4e** (0.08 g, 0.11 mmol), NaH (0.006 g, 0.17 mmol), KO^{t}Bu (cat.), THF (20 ml)], the desired compound was obtained as an off-white solid (0.06 g, 92 % yield). From NMR analysis a 1:1 mixture of isomers was observed. ^{1}H NMR (C_6D_6, 500 MHz): δ 8.20 (s, 1H), 8.11 (s, 8.10), 7.74 (m, 4H), 7.38 (m, 4H), 3.97-3.18 (m, 8H), 2.40-1.60 (m, 32H). ^{13}C NMR (C_6D_6, 125 MHz): δ 246.1, 245.7, 145.0, 144.9, 142.4, 142.2, 138.0, 137.9, 132.8, 132.7, 132.6, 129.1, 129.0, 128.7, 125.9, 125.7, 124.9, 122.0, 121.5, 54.0, 53.9, 47.6, 47.5, 41.3, 36.2, 36.1, 35.9, 35.8, 35.6, 35.5, 35.3, 35.2, 27.4, 27.3, 27.0, 26.5, 26.4, 26.3.

1,3-Bis(2,7-cyclohexylnaphthalen-1-yl)-imidazolin-2-ylidene (5f). Following the general procedure [**4f** (0.40 g, 0.54 mmol), NaH (0.025 g, 0.65 mmol), KO^{t}Bu (cat.), THF (50 ml)], the desired compound was obtained as a pink solid (0.35 g, 99 % yield). From NMR analysis only trace amounts of the *syn* isomer can be detected (less then 5 %). ^{1}H NMR (C_6D_6, 400 MHz): δ 8.22 (s, 2H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.5 Hz 2H), 7.47 (d, *J* = 8.5 Hz 2H), 7.42 (m, 2H), 3.9-3.35 (m, 6H), 2.96 (m, 2H), 2.38-1.30 (m, 40H). ^{13}C NMR (C_6D_6, 100 MHz): δ 245.7, 146.7, 143.9, 137.2, 132.9, 132.8, 129.2, 128.1, 125.3, 125.1, 121.6, 68.2, 54.1, 46.8, 40.5, 35.7, 35.2, 35.1, 34.9, 28.4, 27.8, 27.7, 27.6, 27.2, 26.9, 26.2.

1,3-Bis(2,7-cycloheptylnaphthalen-1-yl)-imidazolin-2-ylidene (5g). Following the general procedure [**4g** (0.10 g, 0.12 mmol), NaH (0.006 g, 0.15 mmol), KO^{t}Bu (cat.), THF (30 ml)], the desired product was obtained as a yellow-orange solid (0.09 g, 91 % yield). From NMR analysis, 5 % of the *syn* isomer can be detected. ^{1}H NMR (C_6D_6, 500 MHz): δ 8.13 (s, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.38 (m, 4H), 3.80 (m, 2H), 3.52 (m, 2H), 3.40 (m, 2H), 3.06 (m, 2H), 2.42-1.3 (m, 48H). ^{13}C NMR (C_6D_6, 125 MHz): δ 246.2, 148.6, 145.8, 136.1, 132.6, 132.5, 129.5, 128.7, 125.5, 125.1, 121.0, 54.2, 49.2, 42.4, 38.2, 37.7, 37.6, 37.3, 29.3, 29.0, 28.7, 28.6, 28.4, 28.1, 28.0, 27.8.

1,3-Bis(2,7-cyclooctylnaphthalen-1-yl)-imidazolin-2-ylidene (5h). Following the general procedure [**4b** (0.10 g, 0.12 mmol), NaH (0.006 g, 0.14 mmol), KO^{t}Bu (cat.), THF (30 ml)], the desired product was obtained as a white solid (0.063 g, 70 % yield). From NMR analysis 5 % of the *syn* isomer can be detected. ^{1}H NMR (C_6D_6, 400 MHz): δ 8.23 (s, 2H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.55(d, *J* = 8.6 Hz, 2H), 7.50 (dd, *J* = 8.4, 1.2 Hz, 2H), 3.97 (br, 2H), 3.77 (br, 2H), 3.57 (br, 2H), 3.27 (br, 2H), 2.40-1.73 (m, 56H). ^{13}C NMR (C_6D_6, 100 MHz): δ 246.6, 149.1, 146.1, 136.2, 132.6, 132.5, 129.4, 128.2, 126.0, 125.5, 121.1, 54.1, 47.2, 40.7, 36.2, 35.4, 34.3, 28.7, 27.9, 27.7, 27.6, 27.0, 26.9, 26.7, 26.6, 26.2, 25.9.

3.7 Additional experimental data

N-(2,6-diisopropylbenzene)-N'-(2-cyclohexylnaphthalen-1-yl)-ethane-1,2-diamine (3i). In a glove box, a Schlenk flask was charged with *rac*-BINAP (0.42 g, 0.68 mmol), $Pd_2(dba)_3$ (0.41 g, 0.45 mmol) NaO^{t}Bu (1.74 g, 18.16 mmol) and toluene (100 ml). The resulting violet suspension was stirred at room temperature for 10 minutes and then 1-bromo-2-cyclohexyl naphthalene (2.89 g, 9.98 mmol) was added. After another 5 minutes **2i** (2.00 g, 9.08 mmol) was added, the flask was taken out of the glovebox, connected to a condenser and the suspension was refluxed for 18 hours. The mixture was cooled to room temperature and then passed through a celite filter to eliminate the inorganic salts. After evaporation of the solvent the obtained oil was purified by silica gel chromatography (eluent: hexane-CH_2Cl_2 4:1 to 1:1) to yield the

desired product as a white solid (1.50 g, 38 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.28 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.53-7.42 (m, 3H), 7.18-7.10 (m, 3H), 3.80-3.60 (s, broad, 2H), 3.45-3.37 (m, 4 H), 3.27 (t, *J* = 6 Hz, 2H), 3.14 (m, 1H) 1.95-1.30 (m, 22H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.9, 136.6, 133.3, 129.6, 128.4, 125.7, 125.3, 125.2, 124.2, 123.8, 123.7, 123.5 52.5, 52.3, 39.0, 34.5, 28.0, 27.4, 26.5, 24.5. HRMS (ESI) *m/z* calcd for $C_{30}H_{40}N_2$: 428.3191. Found: 429.3263 [M+1].

1-(2,6-diisopropylbenzen-1-yl)-3-((2-cyclohexyl)naphthalene1-yl)-imidazolinium tetrafluoroborate (4i). To a Schlenk tube containing **3i** (0.61 g, 1.42 mmol) and NH_4BF_4 (0.21 g, 1.99 mmol), was added $(EtO)_3CH$ (15 ml). To this suspension was added formic acid (3 drops) and the mixture was heated at 110˚C for 2 hours. After this time a lot of sticky yellow solid was present. The suspension was cooled to RT and filtered. The filtrate was washed with 100 ml of Et_2O and dried. It was then purified by silica gel chromatography (eluent: Hexane to CH_2Cl_2 to CH_2Cl_2-MeOH 5:1) to give the desired product as a white powder (0.47 g, 63 % yield). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.52 (s 1H), 8.18 (d, *J* = 8.8 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.79 (t, *J* = 6.8 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.68 (t, *J* = 7.3 Hz, 1H), 7.57 (m, 1H), 7.45 (d, *J* = 7.7 Hz, 2H), 4.85-4.45 (m, 4H), 3.35 (m, 2H), 3.12 (m, 1H), 2.91 (m, 1H), 1.95-1.2 (m, 22H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 161.9, 146.1, 146.0, 143.1, 132.4, 131.2, 130.9, 130.0, 129.3, 128.9, 128.7, 128.5, 128.2, 127.2, 126.8, 125.1, 124.9, 124.8, 121.1, 54.0, 53.1, 33.9, 32.5, 28.2, 26.2, 26.0, 25.2, 25.0, 24.8, 23.5, 23.0. ^{19}F NMR (DMSO-d_6, 376 MHz): δ -148.29, -148.35. HRMS (ESI) *m/z* calcd for $C_{31}H_{39}BF_4N_2$: 526.3142. Found: 439.3109 [M-BF_4].

1,3-Bis(2-(4-heptyl)naphthalen-1-yl)-imidazolin-2-ylidene (5i). To a suspension of **5a** (0.45 g, 0.85 mmol) in dry THF (50 ml) under nitrogen, NaH (55 to 65 % suspension in mineral oil, 0.027 g, 1.11 mmol) and a catalytic amount of KO^{t}Bu were added. The resulting mixture was stirred at room temperature for 15 h. It was then slowly filtered through celite to eliminate the inorganic salts. After evaporation of the solvent, the desired product was obtained as a slightly pink solid (0.37 g, 98 % yield).

^{1}H NMR (C_6D_6, 400 MHz): δ 8.21 (d, *J* = 8.2 Hz, 2H), 7.74 (m, 2H), 7.49 (m, 2H), 7.35 (m, 2H), 7.25 (d, *J* = 7.8 Hz, 2H), 3.68-3.29 (m, 7H), 2.25 (d, *J* = 5.1 Hz, 2H), 1.98-1.30 (m, 21H). ^{13}C NMR (C_6D_6, 100 MHz): δ 245.5, 147.8, 147.7, 143.3, 139.8, 137.5, 134.1, 132.9, 127.0, 125.9, 125.6, 124.5, 125.7, 124.2, 54.3, 53.9, 40.1, 34.8, 34.5, 29.5, 29.2, 28.1, 27.8, 27.0, 25.7, 25.6, 24.4, 23.9.

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CHAPTER FOUR

Efficient Ring-Closing Metathesis of Alkenyl Bromides: The Importance of Protecting the Catalyst during the Olefin Approach.

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Abstract: We present the first productive ring-closing metathesis reaction that leads to the construction of cyclic alkenyl bromides. Efficient catalysis employing commercially available Grubbs II catalyst is possible through appropriate modification of the starting bromoalkene moiety.

The advent of alkylidene-based ruthenium metathesis catalysts featuring high functional group tolerance greatly contributed to the affirmation of alkene metathesis as one of the most important tools to manipulate a C-C double bond.[1] In particular RCM (ring-closing metathesis) has been widely explored and applied in the synthesis of complex natural products.[2] Less developed, but highly desirable, are versions of this reaction in which one of the two olefins bears heteroatom substituents. To date, a number of dienes containing enol ethers and enamines have been studied,[3] but good results in RCM were only obtained with high catalyst loadings and the applicability is restricted to a limited number of substrates. The synthesis of cyclic alkenyl halides, which could subsequently undergo an array of coupling reactions, represents another appealing version of the RCM reaction. Pioneering work in this field has been reported by the Weinreb group,[4a,b] who have shown that cyclic chloroalkenes could indeed be generated, albeit high catalyst loadings were again necessary for acceptable reactivity (10 mol %). This methodology has more recently been employed by Grubbs and Stoltz et al. in the successful synthesis of a specific natural compound.[4c,d] Unfortunately, the more useful alkenyl bromide substrates are known to be

completely inactive with both Schrock- type as well as first- and second-generation Grubbs-type catalysts.[5,6]

In this report, we describe our effort toward the synthesis of carbo- and heterocyclic five-, six-, and seven-membered alkenyl halides via the RCM reaction of the corresponding dienes. Specifically, we show how appropriate protection of the starting alkenyl halide group not only leads to efficient RCM of alkenyl chlorides but also enables the unprecedented and highly efficient construction of cyclic bromoalkenes.

Initial exploratory studies were carried out with malonate-derived alkenyl bromide **1**. As previously reported,[4a,5] both **GI** (Grubbs I) and **GII** (Grubbs II) were completely ineffective for the RCM of **1** as were **HovII** (Hoveyda-Grubbs II) and **BleII** (Blechert II).[7] To possibly gain insight into what prevents catalytic turnover with **1**, we mixed equimolar amounts of **1** and **GII** in C_6D_6 and compared results with a mixture of **GII** and the analogous substrate (**2**) that lacks the second terminal olefin unit (Figure 1). Rather unexpectedly, NMR spectroscopy of this latter mixture did not show appreciable amounts of decomposition of **GII** (and of **2**) over a period of 2 days, whereas substrate **1** was able to completely destroy the precatalyst. During the course of the reaction, a color change to red-brown was observed with concomitant formation of a white precipitate which when analyzed turned out to be clean SIMes·HBr.[8,9] Another byproduct identified in solution and in nearly stoichiometric quantity (>90% against an internal standard) after the reaction was styrene.

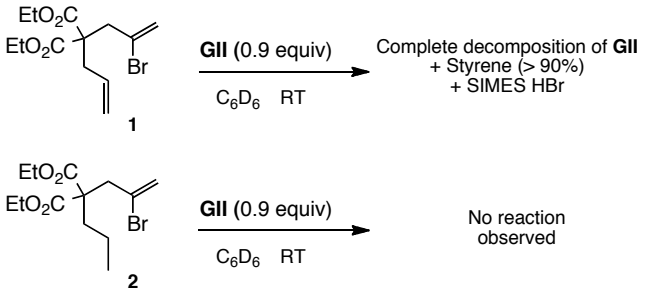


Figure 1. Stoichiometric reactivity of model substrates **1** and **2**.

While the overall mechanism by which **GII** decomposes is speculative at this point, the generation of styrene (and the lack of reactivity between **2** and **GII**) strongly

points to a reaction scenario where initial cross metathesis of the unsubstituted olefin in **1** with the benzylidene moiety of **GII** preceeds decomposition of the catalyst.[10] This in turn would mean that the alkenyl bromide unit only reacts irreversibly with the active ruthenium species when it is forced into close proximity to the metal center.[11] Given these unexpectedly insightful stoichiometric studies, we reasoned that, by simply introducing one or two substituents to the terminal position of the bromoalkene, we could reduce its ability to destroy the catalyst and be able to catalytically generate cyclic bromoalkenes via RCM.[12,13]

Table 1. Influence of Olefin Substitution on Catalytic Activity[a]

1,3,4,5,6 **5a**

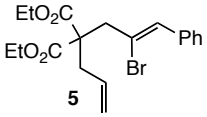
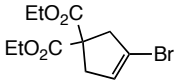
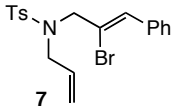
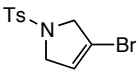
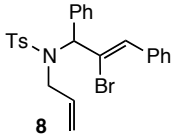
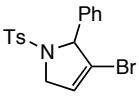
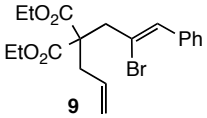
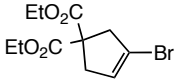
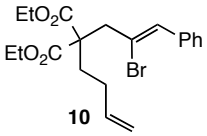
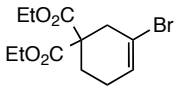
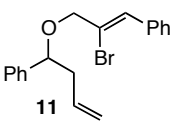
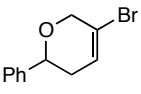
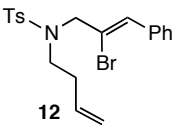
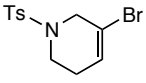
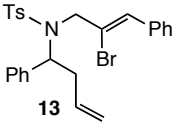
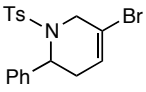
entry	R_1	R_2	mol % **GII**	solvent	*T* (°C)	*t* (h)	yield (%)[c]
1 (**1**)	H	H	2	benzene	60	24	0
2 (**3**)	Me	Me	2	benzene	60	24	0
3 (**4**)	Me	H	2	benzene	60	24	70
4 (**5**)	Ph	H	2	benzene	60	0.5	>98 (90)
5 (**6**)	H	Ph	2	benzene	60	24	0

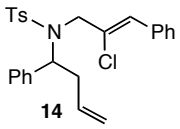
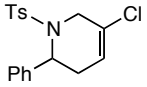
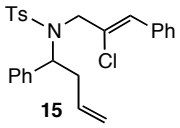
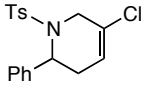
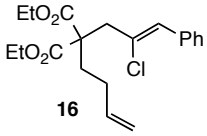
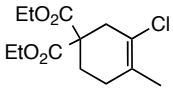
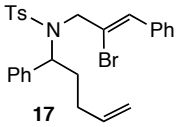
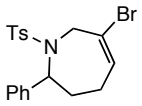
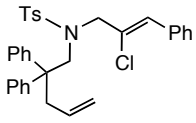
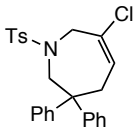
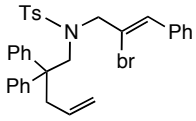
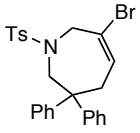
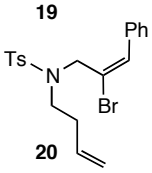
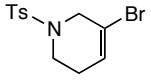
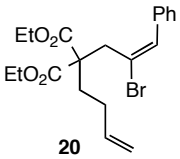
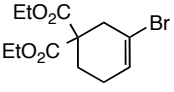
[a] All the reactions were performed with a 0.1 M substrate concentration. The substrate was added via syringe to a solution of catalyst preheated in an oil bath for 2 min. [b] For a screening of different solvents and catalysts, see the Supporting infomation. [c] Yields based on NMR analysis. Isolated yiled in parenthesis.

As a first attempt, we tested a substrate featuring a geminal dimethyl substitution (Table 1, entry 2) that proved to be unreactive in RCM, most probably due to the low propensity of a tetrasubstituted olefin to approach the metal center and bind to it. In contrast, the introduction of a single substituent *Z* to the bromine atom turned out to be highly beneficial. In the presence of a methyl group (Table 1, entry 3) formation of a substantial amount of product was observed from NMR analysis;[14] when a substrate featuring a *Z*-configured terminal phenyl group was employed, full conversion was observed and product **5a** was obtained in 90% isolated yield using 2 mol % of **GII** (Table 1, entry 4). Mechanistically most relevant and in line with the idea of correctly

protecting the alkenyl bromide during its approach to the metal, incorporation of a terminal phenyl group *E* to the halide (Table 1, entry 5) did not lead to any product formation under otherwise identical reaction conditions.[15]

Table 2. RCM Reactions Generating Cyclic Alkenyl Bromides and Chlorides

entry[a]	substrate[b]	product	GII (mol %)	solvent	*t* (h)	yield (%)[c]
1	 **5**	 **5a**	2	Benzene	0.5	90
2	 **7**	 **7a**	2	Benzene	1.5	64
3	 **8**	 **8a**	2	Benzene	1.5	76
4	 **9**	 **9a**	2	Benzene	0.5	96
5	 **10**	 **10a**	2 0.5 0.1	Benzene Benzene Benzene	0.5 2 2	96 92 75
6	 **11**	 **11a**	2	Benzene	0.5	94
7	 **12**	 **12a**	2	Benzene	1.5	95
8	 **13**	 **13a**	2	Benzene	2	95

entry[a]	substrate[b]	product	GII (mol %)	solvent	*t* (h)	yield (%)[c]
9	 **14**	 **14a**	2	Benzene	2	97
10	 **15**	 **15a**	5	CH_2Cl_2[d]	4	81
11	 **16**	 **16a**	5	CH_2Cl_2[d]	14	92
12	 **17**	 **17a**	5	CH_2Cl_2[d]	24	0[d]
13	 **18**	 **18a**	5	CH_2Cl_2[d]	3	76
14	 **19**	 **19a**	5	CH_2Cl_2[d]	3	67
15	 **20**	 **12a**	2	Benzene	5	Trace
16	 **20**	 **12a**	2	Benzene	5	Trace

[a] All The reaction were performed using 0.16 mmold of substrate with a 0.1 M substrate concentration except entries 12-14 (0.01 M). [b] Shelf lives of all compounds at -25 °C are at least 5 months without decomposition. [c] Isolated yield after column chromatography. [d] Reactions performed in benzene gave slightly lower yields. The main producto of the reaction was compound **13a**.

The scope of the reaction was then explored with a wider range of bromoalkene derivatives, and the results are summarized in Table 2. Overall, five-membered and especially six-membered rings were generated in good to excellent isolated yields within short reaction times. Indeed, less than 2 mol % of **GII** seem to suffice for efficient ring closing as evidenced from data collected for substrate **10** (Table 2, entry 5). Vastly improved results as compared to data in the literature4a were obtained when applying the same concept to the construction of representative cyclic alkenyl chlorides **9a** and **14a** (Table 2, entries 4 and 9). Likewise, the synthesis of six-membered tetrasubstituted cyclic chloroalkenes **15a** and **16a** proceeded with remarkable ease and in high yield when employing a higher catalyst loading (Table 2, entries 10 and 11).[16] Unfortunately, an attempt to generate the analogous tetra-substituted cyclic alkenyl bromide gave only trace amounts of product. For the synthesis of seven- membered rings (substrates **17**-**19**), the disposition of the substituents proved to be important and efficient catalysis was only possible with substrates **18** and **19**, where a stronger Thorp-Ingold effect is to be expected (Table 2, entries 13 and 14).[17] Indeed, when trying to ring-close substrate **17**, relatively clean conversion (50% isolated yield) to the six-membered product **13a** was observed, meaning that an unusually efficient olefin isomerization step occurs before the expected metathetical ring closure.[18]

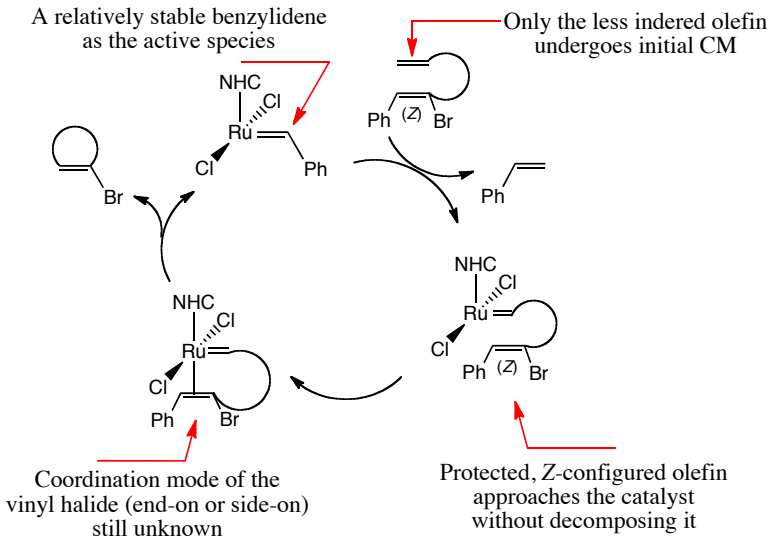


Figure 2. Proposed catalytic cycle for the RCM of bromoalkenes.

The last two entries in Table 2 (15 and 16) again underline the importance of correctly substituting the starting alkenyl bromide and the strikingly different reactivity of the resulting diene, as both *E*-configured olefins **19** and **20** did not generate the desired RCM products.[19]

In conclusion, we have developed a catalytic method (Figure 2) to access cyclic alkenyl bromides via the ruthenium-catalyzed ring-closing metathesis reaction using synthetically useful catalyst loadings of **GII** (Grubbs II). The starting diene compounds are easily accessible and should make the present protocol attractive as a methodology for the construction of more elaborate molecular structures.

The concept of sterically protecting double bonds that would otherwise irreversibly react and deactivate metathesis-active catalysts should not be applicable to only alkenyl halides, and studies aimed at developing this idea further are currently underway.

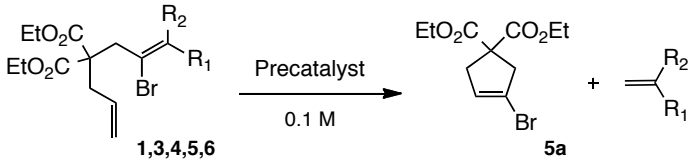
4.1 Experimental section

General procedure: All reactions were carried out under nitrogen atmosphere using standard Schlenk-lines or glovebox (Mecaplex or Innovative Technology). Solvents (THF, CH_2Cl_2, pentane and Et_2O) were purged through alumina columns in a solvent purification system (Innovation Technology). Toluene was distilled from Na or Na/benzophenone. Benzene (HPLC quality) was degassed and stored in a glovebox over molecular sieves. Dry DMF was purchased from ACROS and stored in a glovebox. Solvent for NMR spectroscopy were degassed with nitrogen and dried over molecular sieves. NMR spectra were collected on an AV2 400 or AV2 500 MHz Bruker spectrometer. Chemical shift are given in ppm. The spectra are calibrated to the residual ^{1}H and ^{13}C signals of the solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), doublet-doublet (dd), quintet (quint), septet (sept), multiplet (m), and broad (br). High-resolution electrospray ionization mass spectrosmetry was performed on a *FinniganMAT 900* (Finnigan MAT95, San Jose, CA; USA) double-focusing magnetic sector mass spectrometer (geometry BE). GC-MS analysis was done on a Finnigan Voyager GC8000 Top. Infrared spectroscopy was performed on a Jasco FT/IR-4100. All commercially

available products were used as received except for 2,3-dibromopropene (Sigma Aldrich, Technical grade 85%) that was fractionally distilled.

Screening of reaction conditions

Table 1. Preliminary screening of the reaction conditions[a]



1,3,4,5,6 **5a**

entry	R_1	R_2	precatalyst (mol %)	solvent	T (°C)	*t* (h)	yield (%)[b]
1 (**1**)	H	H	**GII** (2)	Benzene	60	24	0
2 (**1**)	H	H	**HovII** (2)	Benzene	60	24	0
3 (**1**)	H	H	**BleII** (2)	Benzene	60	24	0
4 (**3**)	Me	Me	**GII** (2)	Benzene	60	24	0
5 (**4**)	Me	H	**GII** (2)	Benzene	60	24	70
6 (**5**)	Ph	H	**GII** (2)	Benzene	60	0.5	100 (90)
7 (**5**)	Ph	H	**GI** (5)	Benzene	60	24	< 5
8 (**5**)	Ph	H	**HovII** (2)	Benzene	60	24	70 (61)
9 (**5**)	Ph	H	**BleII** (2)	Benzene	60	0.5	100 (87)
10 (**5**)	Ph	H	**GII** (2)	Benzene	60	24	100 (80)[c]
11 (**5**)	Ph	H	**GII** (2)	Benzene	27	24	< 5
12 (**5**)	Ph	H	**BleII** (2)	Benzene	27	24	< 5
13 (**5**)	Ph	H	**GII** (2)	Toluene	60	0.5	100 (73)
14 (**5**)	Ph	H	**GII** (2)	CH_2Cl_2	60	0.5	100 (85)
14 (**6**)	H	Ph	**GII** (2)	Benzene	60	0.5	0

[a] All the reactions were performed with a 0.1 M substrate concentration. The substrate was added via siringe to a solution of catalyst preheated in an oil bath for 2 minutes. [b] Yields based on NMR analysis. Isolated yields in brackets. [c] Substrate mixed with catalyst at room temperature and then heated at 65°C

Stechiometric experiments

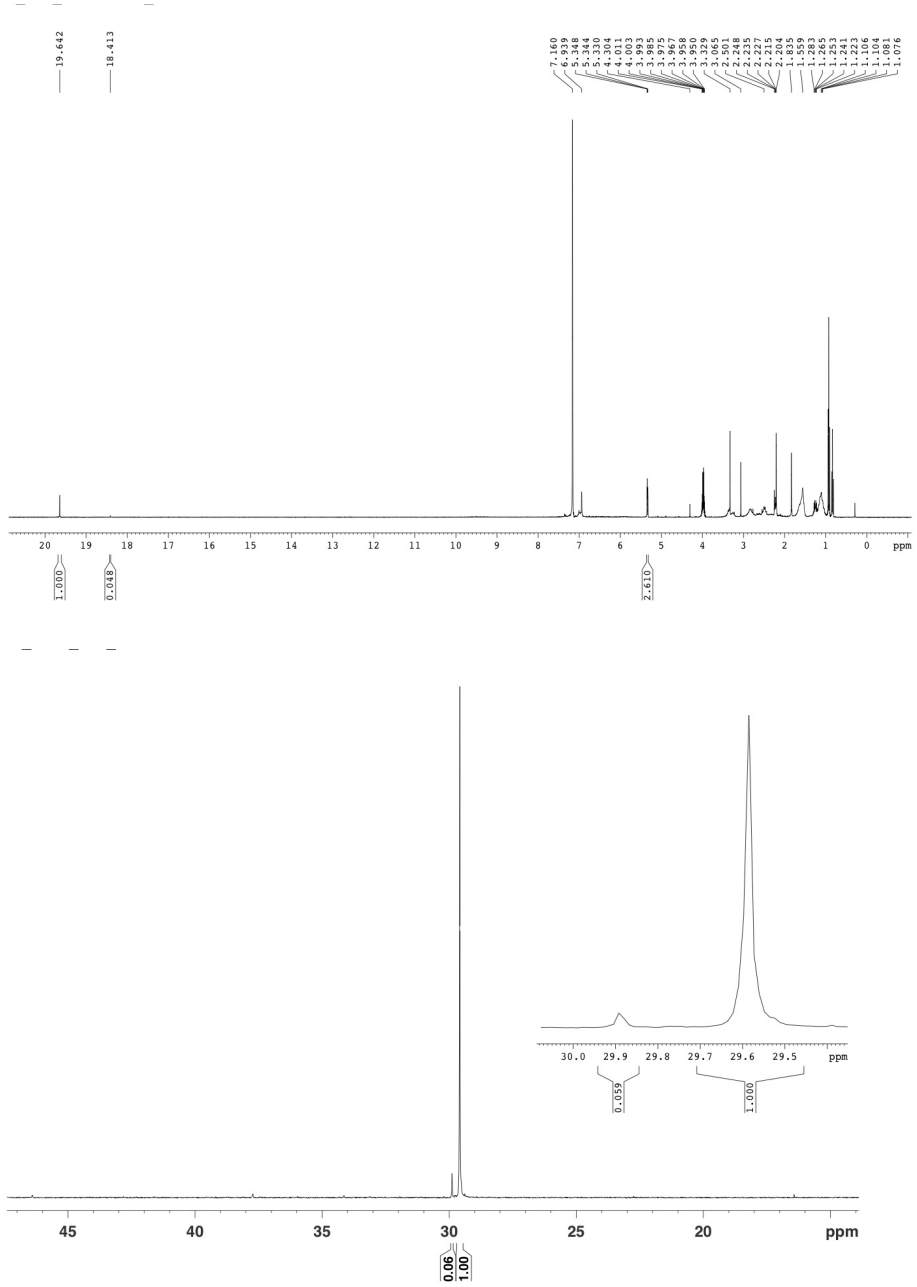


Figure 1. ^{1}H (up) and ^{31}P (down) NMR of the reaction between 1.3 eq of **2** and 1 eq of **GII** in C_6D_6 recorded after 40 h at room temperature under nitrogen. Decomposition of the catalyst is between 5 and 6 %.

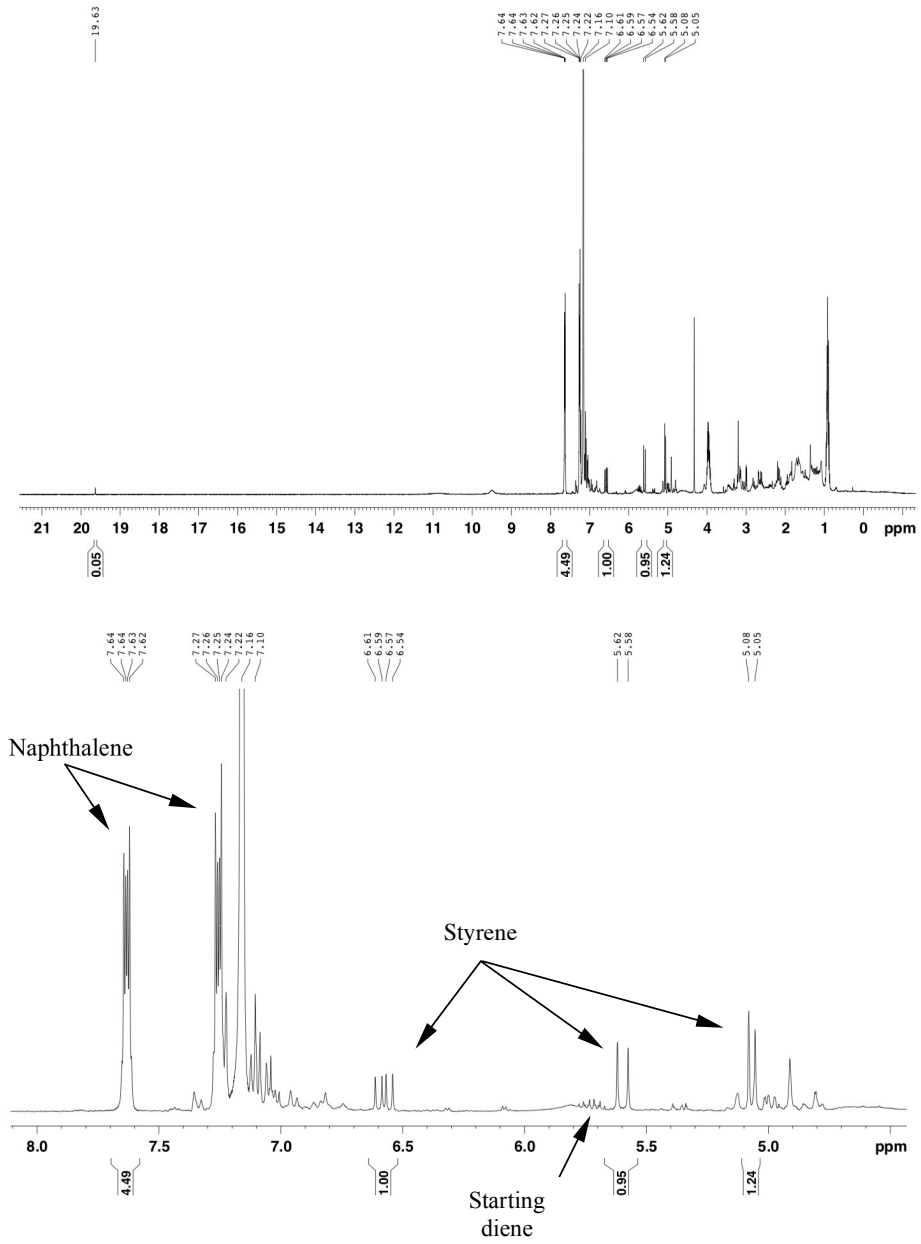
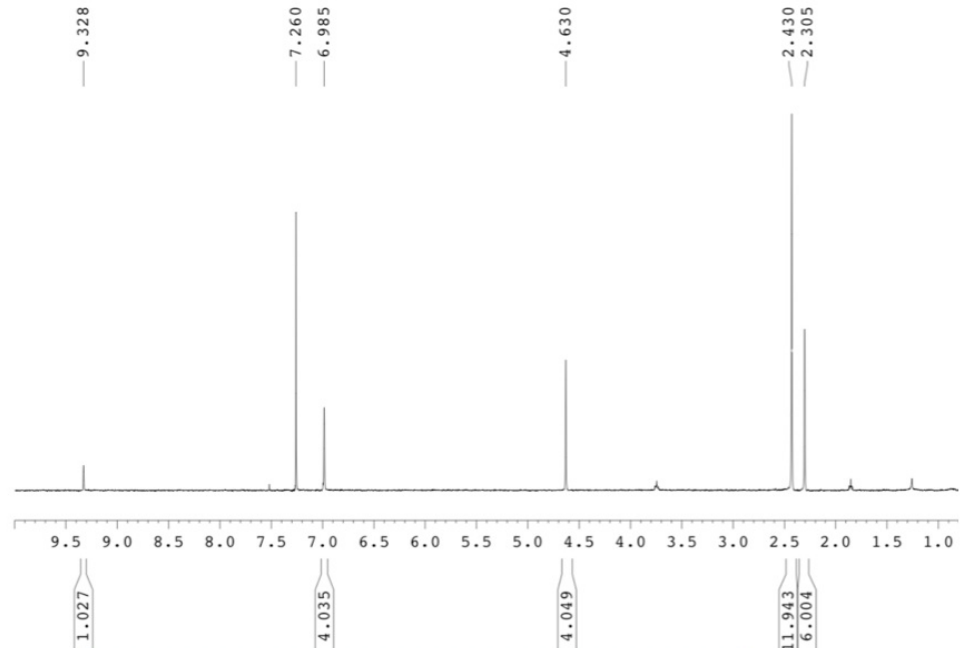
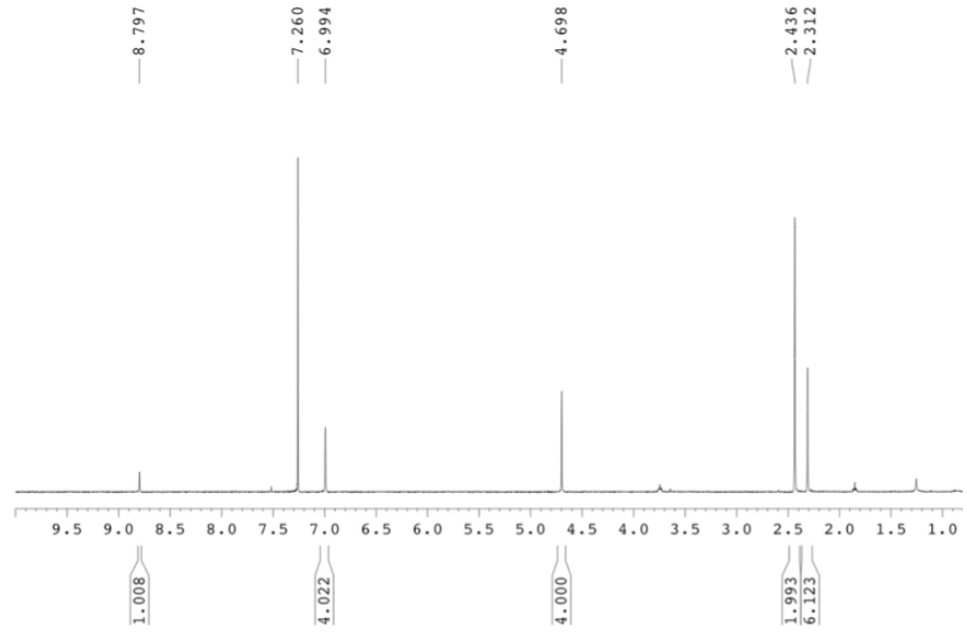


Figure 2. ^{1}H NMR of the reaction between 1.2 eq of **1** and 1 eq of **GII** in C_6D_6 recorded after 24 h at room temperature under nitrogen. 1 eq of naphthalene was used as internal standard (added at the end of the reaction, before NMR analysis). **GII** is almost completely decomposed. Formation of styrene (~ 0.9 eq) is observed. Unreacted **2** is still present.

MG_1H_SIMES_HCl_diluted



MG_1H_HBr_diluted



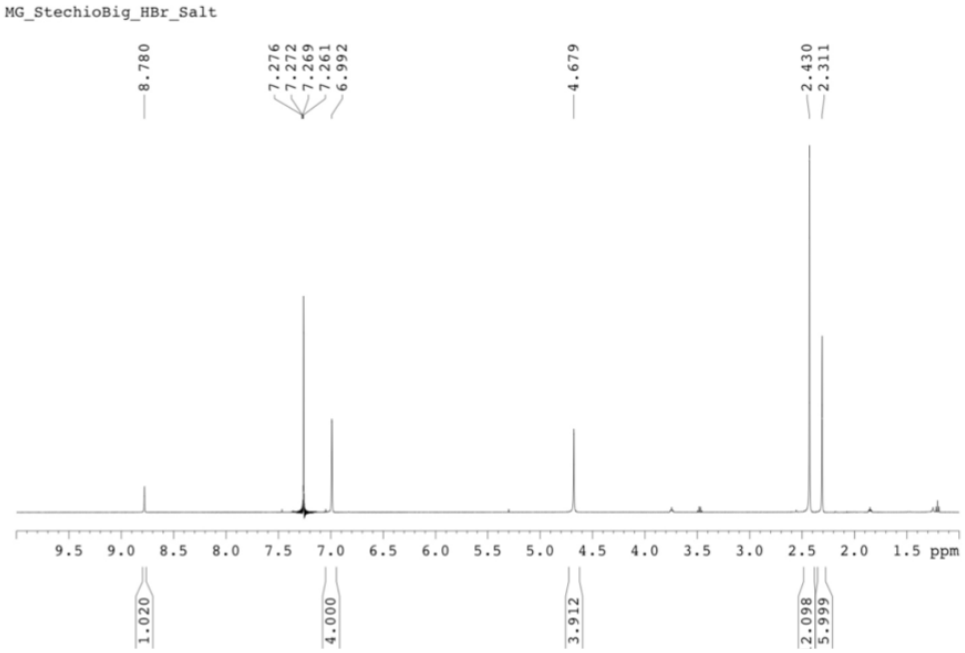
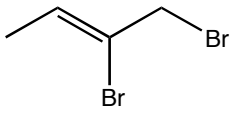


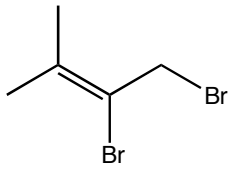
Figure 3. Determination of the NHC salt counterion (^{1}H NMR). Reference SIMes·HCl and HBr (page before) and SIMes·HBr obtained from the reaction of **1** with **GII** (below).

Experimental section: synthesis of substrates.

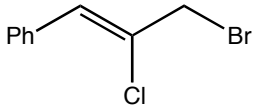


(*Z*)-1,2-Dibromo-2-butene (I): A mixture of *trans*-α-Bromocrotyl alcohol[20] (1.50 g, 9.93 mmol) and tetrabromocarbon (4.28 g, 12.91 mmol) in CH_3CN (40 ml) was cooled to 0°C and then powdered triphenylphosphine (3.39 g, 12.91 mmol) was added portionwise. The transparent mixture obtained was stirred at room temperature until complete conversion was observed from TLC (Hexane - Et_2O 10:1). The solvent was distilled off to give a viscous yellow oil to which hexane (3 ml) was added. The resulting suspension was sonicated for 5 minutes and then directly loaded on a silica gel filter (eluent: Hexane). Compound **I** was obtained in quantitative yield as a transparent oil (traces of $CHBr_3$ were present from ^{1}H-NMR analysis). IR (film):

1647, 1298, 1210, 943, 909, 673, 617 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.18 (m, 1H), 4.32 (s, 2H), 1.76 (d, *J* = 7.2 Hz, 3H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 129.8, 123.8, 39.1, 17.5 ppm. HRMS (ESI) calcd for $C_4H_6Br_2$: 211.8836. Found 211.8836.

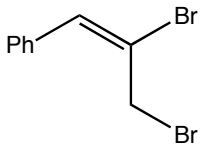


1,2-Dibromo-3-methyl-2-butene (II): A solution of 2-bromo-3-methyl-buten-1-ol[21] (0.50 g, 3.00 mmol) in CH_2Cl_2 (20 ml) was cooled to -20°C and then powdered triphenylphosphine (0.94 g, 3.6 mmol) was added. To the resulting mixture was added solid N-bromo succinimide (0.59 g, 3.3 mmol) and the solution was stirred until from TLC (Hexane - Et_2O 10:1) the reaction was complete (2h). Water was added (20 ml) and the organic layer was extracted with CH_2Cl_2 (2x50 ml). After evaporation of the solvent the resulting yellow oil was subjected to silica gel chromatography (eluent: Hexane) to give the desired product (0.46 g, 67% yield). The analytical data were consistent with the one reported in literature.[22]

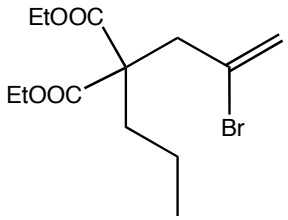


(*Z*)-(2-Chloro-3-bromopropenyl)benzene (III): A mixture of (*Z*)-2-bromo-3-phenylprop-2-en-1-ol[23] (1.10 g, 6.52 mmol) and tetrabromocarbon (2.60 g, 7.83 mmol) in CH_3CN (30 ml) was cooled to 0°C and then powdered triphenylphosphine (2.05 g, 7.83 mmol) was added portionwise. The resulting transparent mixture was stirred at room temperature until complete conversion was observed from TLC (eluent: Hexane-Et_2O 10:1). After distillation of the solvent a yellow oil was obtained. Hexane (3 ml) was added and the resulting suspension was sonicated for 5 minutes and then directly loaded on a silica gel filter (eluent: Hexane). Compound **3** was obtained in quantitative yield as a transparent oil. From NMR analysis traces of $CHBr_3$ are present. They can be easily eliminated via distillation (35 °C, 0.01 mbar).

IR (film): 3055, 3025, 1631, 1597, 1574, 1491, 1447, 1242, 1345, 1288, 1208, 1286, 1158, 1135, 1106, 1093, 1070, 1030, 919, 899, 863, 824, 752, 690, 656, 643, 621, 613, 524, 480 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, *J* = 7.8 Hz, 2H), 7.4 (m, 3H), 6.87 (s, 1H), 4.32 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 134.0, 132.6, 129.5, 129.2, 129.0, 128.5, 38.8. HRMS (EI) calcd for C_9H_8ClBr: 229.9498. Found 229.9499.

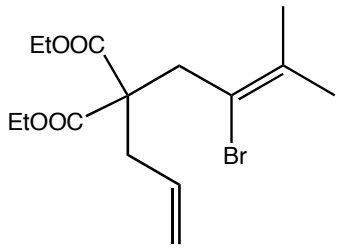


(*E*)-(2,3-Dibromopropenyl)-benzene (IV): To a solution of (*Z*)-(2,3-dibromoprop-1-enyl)benzene[24] (1.00 g, 3.62 mmol) in 3 ml of $CHCl_3$ was added a catalytic amount of I_2. The obtained mixture was stirred until a light pink uniform solution is obtained and then it was exposed for 3 h to sunlight. After this time from TLC (eluent: Hexane) an almost 1:1 mixture of *E* and *Z* product was obtained. The solvent was distilled at room temperature and the obtained orange oil was loaded into a silica gel column (eluent: Hexane). Compound **4** (300 mg, 1.09 mmol, 30% yield) was obtained as transparent oil that rapidly solidifies at low temperature. From NMR analysis about 5% of *Z* isomer is present. The starting material was recovered after purification (0.65 g, 2.35 mmol). The obtained analytical data (IR and MS) were consistent with the one reported in literature.[25] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 - 745 (m, 5H), 7.12 (s, 1H), 4.40 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.0, 135.5, 129.1, 128.2 122.8, 35.4.

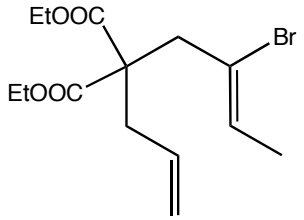


Diethyl-2-(2-bromo-prop-2-enyl) malonate (2): Following the procedure described

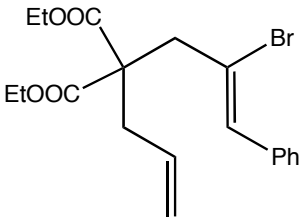
for compound **5** and starting from diethyl-2-propyl malonate (1.00 g, 5.31 mmol), 2,3-dibromopropene (1.27 g, 6.37 mmol), NaOEt (0.43 g, 6.37 mmol) and THF (40 ml) the desired product was obtained after silica gel chromatography (eluent: Hexane - CH_2Cl_2 30:1) as a transparent oil (1.40 g, 86 % yield). IR (film): 2964, 2937, 1731, 1625, 1465, 1446, 1367, 1281, 1257, 1219, 1193, 1146, 1126, 1096, 1042, 1027, 913, 899, 856 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 5.63 (s, 1H), 5.57 (m, 1H), 4.18 (m, 4H), 3.15 (s, 2H), 1.95 (m, 2H), 1.22 (m, 8H), 0.97 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 127.8, 121.6, 61.7, 57.4, 43.1, 33.7, 17.6, 14.4, 14.2. HRMS (ESI) calcd for $C_{13}H_{21}BrO_4$: 320.0623. Found 343.0524.



Diethyl-2-allyl-2'-(2-bromo-3-methyl-but-2-enyl) malonate (3): Following the procedure described for compound **5** and starting from diethyl-2-allyl malonate (0.35 g, 1.76 mmol), **II** (0.40 g, 1.76 mmol), NaOEt (0.14 g, 2.11 mmol) and THF (25 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - CH_2Cl_2 1:1) as a transparent oil (0.55 g, 90 % yield). IR (film): 3075, 2983, 1731, 1654, 1642, 1464, 1440, 1387, 1366, 1324, 1300, 1276, 1247, 1209, 1189, 1129, 1095, 1051, 1039, 944, 858, 791, 691, 603 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 5.72 (m, 1H), 5.05 (m, 2H), 4.15 (m, 4H), 3.28 (m, 2H), 2.72 (d, *J* = 7.0 Hz, 2H), 1.86 (s, 3H), 1.76 (s, 3H), 1.24 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.0, 135.6, 133.2, 119.1, 115.5, 61.6, 58.1, 39.5, 36.8, 26.0, 21.7, 14.2. HRMS (ESI) calcd for $C_{15}H_{23}BrO_4$: 346.0780. Found 369.0679. [M+Na].

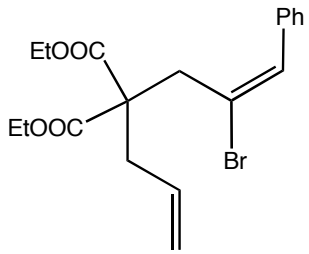


Diethyl-2-allyl-2'-((*Z*)-2-bromo-2-butenyl) malonate (4): Following the procedure described for compound **5** and starting from diethyl-2-allyl malonate (0.40 g, 2.00 mmol), **I** (0.51 g, 2.4 mmol), NaOEt (0.15 g, 2.20 mmol) and THF (25 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 30:1) as a transparent oil (0.67 g, 95 % yield). IR (film): 3077, 2981, 2936, 1730, 1654, 1642, 1464, 1441, 1389, 1366, 1326, 1300, 1276, 1247, 1211, 1187, 1130, 1095, 1052, 1037, 944, 922, 858, 821, 791, 691, 603, 570 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 5.85 (m, 1H), 5.77 (m, 1H), 5.10 (m, 2H), 4.18 (m, 4H), 3.15 (s, 2H), 2.72 (d, *J* = 7.3 Hz, 2H), 1.72 (d, *J* = 6.5 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 132.7, 129.1, 122.1, 119.4, 61.7, 57.5, 43.4, 36.3, 17.3, 14.2. HRMS (ESI) calcd for $C_{14}H_{21}BrO_4$: 332.0623. Found 355.0514 [M+Na].

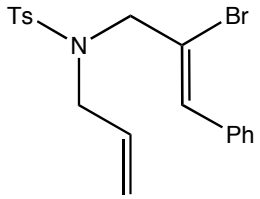


Diethyl-2-allyl-2'-((*Z*)-3-phenyl-2-bromo-2-propenyl) malonate (5): To a solution of diethyl allyl malonate (0.50 g, 2.50 mmol) in dry THF (5 ml) was added NaOEt (0.19 g, 2.75 mmol). The obtained mixture was stirred at room temperature until almost all the NaOEt was dissolved and then (*Z*)-(2,3-Dibromoprop-1-enyl)-benzene was added dropwise as a solution in THF (1 ml). From TLC analysis after 1 h at room temperature the reaction is complete. A solution of HCl (5% in water) was added (20 ml) and the organic layer was extracted with Et_2O (3x20 ml). After evaporation of the solvent a yellow oil was obtained. This was subjected to silica gel chromatography purification (eluent: Hexane to Hexane - Et_2O 30:1) to give the desired product

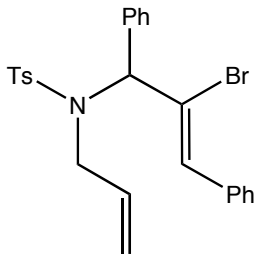
(transparent oil, 0.61 g, 62 % yield). From NMR analysis about 5% of E isomer was detected. IR (film): 3079, 2980, 2936, 1730, 1640, 1492, 1464, 1445, 1389, 1366, 1325, 1293, 1274, 1244, 1211, 1186, 1142, 1095, 1083, 1070, 1032, 999, 920, 860, 794, 750, 695, 553 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.52 (m, 2H), 7.37-7.26 (m, 3H), 6.85 (s, 1H), 5.74 (m, 1H), 5.17 (m, 2H), 4.22 (m, 4H), 3.35 (s, 2H), 2.84 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 135.9, 132.9, 132.6, 129.1, 128.3, 128.2, 120.3, 119.7, 61.8, 57.6, 45.0, 36.5, 14.3. HRMS (ESI) calcd for $C_{19}H_{23}BrO_4$: 394.0780. Found 417.0672 [M+Na].



Diethyl-2-allyl-2'-((*E*)-3-phenyl-2-bromo-2-propenyl) malonate (6): Following the procedure described for compound **5** and starting from diethyl-2-allyl malonate (0.18 g, 0.88 mmol), **IV** (0.27 g, 0.98 mmol), NaOEt (0.07 g, 0.98 mmol) and THF (10 ml), the desired product was obtained after silica gel chromatography (eluent: CH_2Cl_2) as a transparent oil (0.33 g, 95 % yield). IR (film): 2983, 1728, 1642, 1625, 1445, 1368, 1267, 1184, 1079, 1034, 913, 861, 754, 702, 554 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 (m, 2H), 7.30-7.20 (m, 3H), 7.18 (s, 1H), 5.14 (m, 1H), 4.86 (m, 1H), 4.75 (m, 1H), 4.12 (m, 4H), 3.50 (s, 2H), 2.67 (m, 2H), 1.20 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.5, 137.3, 136.1, 132.2, 128.9, 128.6, 127.8, 123.5, 119.2, 62.0, 57.7, 37.3, 36.4, 14.1. HRMS (ESI) calcd for $C_{19}H_{23}BrO_4$: 394.0780. Found 417.0676 [M+Na].



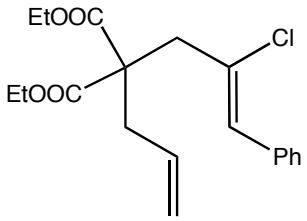
N-Allyl-N-((*Z*)-3-phenyl-2-bromo-2-propenyl)-*p*-toluensulfonamide (7): To a solution of N-allyl-*p*-toluenesulfonamide[26] (0.50 g, 2.38 mmol) in dry DMF (10 ml) cooled to 0°C was added NaH (55-65 % in mineral oil, 0.11 g, 2.85 mmol). The resulting white suspension was stirred for 15 min at this temperature and then (*Z*)-(2,3-Dibromoprop-1-enyl)-benzene was added dropwise as a solution in dry DMF (5 ml). The color changed rapidly to light yellow and the suspension vanished. From TLC analysis the reaction was completed after 30 min. The reaction mixture was quenched with a solution of NH_4Cl (15 ml) and extracted with Et_2O (2x30 ml). After evaporation of the solvent and silica gel chromatography (eluent: Hexane - Et_2O 7:1) the desired product was obtained as light yellow oil. To further purify the substrate crystallization from hot hexane was necessary. The product was then obtained as white needles (0.86 g, 90 % yield). From NMR analysis 5% of the *E* isomer was present. IR (film): 3083, 3055, 3025, 2980, 2921, 2858, 1639, 1597, 1492, 1445, 1343, 1158, 1091, 991, 907, 863, 814, 749, 694, 663, 585, 547, 522 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 4.8 Hz, 2H), 7.50 (m, 2H), 7.35 – 7.26 (m, 5H), 6.91 (s, 1H), 5.65 (m, 1H), 5.17 (m, 2H), 4.21 (s, 2H), 3.91 (d, J = 6.5 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 137.6, 135.1, 132.6, 130.8, 129.9, 129.2, 128.5, 128.4, 127.6, 120.8, 119.9, 56.0, 50.4, 21.7. HRMS (ESI) calcd for $C_{19}H_{20}BrNO_2S$: 405.0398. Found 428.0875 [M+Na].



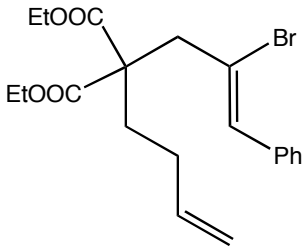
N-Allyl-N-((*Z*)-3-phenyl-2-bromo-2-propenyl)-*p*-toluensulfonamide (8): To a

solution of chalcone (4.00 g, 19.20 mmol) in dry CH_2Cl_2 (50 ml) cooled to 0°C was added Br_2 (3.69 g, 23.04 mmol) dropwise. The obtained orange solution was stirred for 1 h at room temperature and then quenched with a 1 M NH_4Cl water solution (50 ml). It was extracted with CH_2Cl_2 (2x30 ml), dried on $MgSO_4$ and the solvent was removed under reduced pressure. The resulting solid was dissolved in $CHCl_3$ (30 ml) and Et_3N (3.30 g, 32.60 mmol) was added. The obtained mixture was stirred overnight at room temperature. At this point from TLC all the starting material was consumed. A 5 % HCl water solution was added (30 ml) and the solution was extracted with CH_2Cl_2. After column chromatography (eluent: Hexane - Et_2O 10:1 to 4:1) the desired product was obtained as a yellow oil (4.50 g, 82 % yield). All the analytical data obtained matched the ones previously reported in literature.[27] This unsaturated ketone (1.00 g, 3.48 mmol) was dissolved in MeOH (30 ml) and $CeCl_3*7H_2O$ (1.36 g, 3.66 mmol) was added at room temperature. After complete dissolution of the salt, $NaBH_4$ (0.16 g, 4.18 mmol) was added portionwise (caution: gas is rapidly released from the reaction). From TLC all the starting material was consumed after 30 minutes. To the mixture was added a 5 % HCl solution in water (40 ml), it was extracted with Et_2O, dried on $MgSO_4$ and the solvent was evaporated under reduced pressure. The desired product was obtained after silica gel chromatography (eluent: Hexane – Et_2O 9:1) as a clear oil (0.98 g, 97 % yield). All the analytical data obtained matched the ones previously reported in literature.[28] This alcohol (0.28 g, 0.97 mmol) was dissolved in THF (10 ml) and to the obtained mixture, cooled to 0°C, were added PPh_3 (0.25 g, 0.97 mmol) and N-allyl-*p*-toluensulfonamide (0.17 g, 0.81 mmol). DIAD (0.20 g, 0.97 mmol) was then added dropwise dissolved in THF (5 ml). The reaction was stirred at room temperature until from TLC all the starting material was consumed (5 h). Water (20 ml) was then added and the obtained mixture was extracted with Et_2O and dried on $MgSO_4$. After evaporation of the solvent under reduced pressure the resulting yellow oil was purified by silica gel chromatography (eluent: Hexane - Et_2O 9:1). The desired product was obtained as a transparent oil (0.30 g, 77 % yield). IR (film): 2921, 2866, 1630, 1597, 1493, 1455, 1348, 1305, 1291, 1161, 1094, 1076, 1045, 870, 828, 814, 754, 698, 669, 640, 604, 576, 546 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, J = 7.8 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.38 – 7.25 (m, 10H), 6.81 (s, 1H), 6.10 (s, 1H),

4.85 (m, 2H), 3.92 (m, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.8, 136.6, 135.2, 134.9, 131.7, 129.7, 129.5, 129.3, 128.8, 128.5, 128.4, 128.3, 127.9, 123.8, 117.5, 69.7, 49.2, 21.7. HRMS (ESI) calcd for $C_{25}H_{24}BrNO_2S$: 481.0711. Found 504.0611 [M+Na].

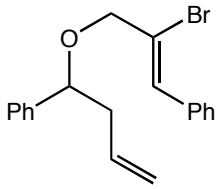


Diethyl-2-allyl-2'-((*Z*)-3-phenyl-2-chloro-2-propenyl) malonate (9): Following the procedure described for compound **5** and starting from diethyl-2-allyl malonate (0.50 g, 2.52 mmol), **III** (0.61 g, 2.64 mmol), NaOEt (0.19 g, 2.77 mmol) and THF (25 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 5:1) as a transparent oil (0.74 g, 84 % yield). IR (film): 2982, 2937, 1732, 1640, 1491, 1445, 1367, 1296, 1244, 1212, 1187, 1143, 1095, 1073, 1032, 920, 861, 752, 693, 648 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, *J* = 7.6 Hz, 2H), 7.38-7.26 (m, 3H), 6.56 (s, 1H), 5.72 (m, 1H), 5.15 (m, 2H), 4.22 (m, 4H), 3.29 (s, 2H), 2.8 (d, *J* = 7.3 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 134.8, 132.6, 129.5, 129.3, 129.0, 128.4, 128.1, 119.7, 61.8, 57.3, 43.5, 36.5, 14.3. HRMS (ESI) calcd for $C_{19}H_{23}ClO_4$: 350.1285. Found 373.1180 [M+Na].

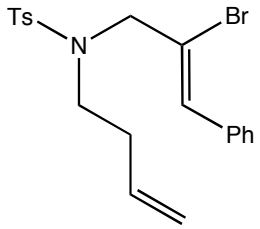


Diethyl-2-(but-2-enyl)-2'-((*Z*)-3-phenyl-2-bromo-2-propenyl) malonate (10): Following the procedure described for compound **5** and starting from diethyl-2-(But-

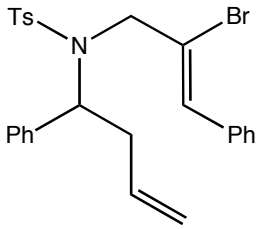
3-enyl) malonate[29] (0.42 g, 1.96 mmol), (*Z*)-(2,3-Dibromoprop-1-enyl)-benzene (0.65 g, 2.35 mmol), NaOEt (0.16 g, 2.35 mmol) and THF (15 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 40:1) as a transparent oil (0.77 g, 97 % yield). IR (film): 3077, 2980, 2939, 1731, 1644, 1447, 1367, 1261, 1203, 1184, 1091, 1032, 917, 861, 752, 696, 555 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51(m, 2H), 7.37-7.26 (m, 3H), 6.82 (s, 1H), 5.78 (m, 1H), 5.01 (m, 2H), 4.22 (m, 4H), 3.37 (s, 2H), 2.1 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 137.5, 135.9, 132.7, 129.1, 128.3, 128.2, 120.5, 115.4, 61.8, 57.6, 44.9, 31.0, 28.7, 14.3. HRMS (ESI) calcd for $C_{20}H_{25}BrO_4$: 408.0936. Found 431.0626 [M+Na].



1-Phenyl-1-((*Z*)-2-bromo-3-phenyl-but-3-enyl)-3-butene (11): Benzaldehyde (0.11 g, 1,00 mmol), (*Z*)-2-bromo-3-phenylprop-2-en-1-ol[24] (0.210 g, 1.00 mmol) and allyl-trimethylsilane (0.14 g, 1.20 mmol) where charged in a 20 ml round bottom flask under nitrogen. To this mixture was added I_2 (0.02 g, 0.10 mmol) and the obtained solution was stirred for 2 h at room temperature. It was then directly subjected to column chromatography purification (eluent: Hexane - CH_2Cl_2 3:1) to give the desired product as colorless oil (0.14 g, 40 % yield). IR (film): 3062, 3025, 2903, 2853, 1641, 1491, 1446, 1352, 1306, 1288, 1263, 1101, 1077, 1026, 997, 916, 858, 751, 693, 612, 593, 546, 515, 485, 425, 401 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60 (m, 2H), 7.40-7.25 (m, 8H), 6.95 (s, 1H), 5.83 (m, 1H), 5.05 (m, 2H), 4.42 (m, 1H), 4.22 (dd, *J* = 1.3 - 13.8 Hz, 1H), 4.03 (dd, *J* = 1.0 - 13.8 Hz, 1H), 2.65 (m, 1H), 2.45 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.5, 135.4, 134.9, 129.3, 129.0, 128.7, 128.4, 128.3, 128.1, 127.1, 122.7, 117.4, 81.5, 74.5, 42.8. HRMS (ESI) calcd for $C_{19}H_{19}BrO$: 342.0619. Found 365.0509 [M+Na].

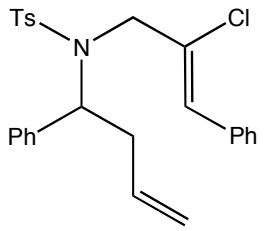


N-(But-3-enyl)-N-((*Z*)-3-phenyl-2-bromo-2-propenyl) - *p*-toluensulfonamide (12): Following the procedure described for compound **7** and starting from N-(But-3-enyl)-*p*-toluensulfonamide[30] (0.30 g, 1.25 mmol), (*Z*)-(2,3-Dibromoprop-1-enyl)-benzene (0.29 g, 1.05 mmol), NaH (0.04 g, 1.05 mmol) and DMF (10 ml) the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 9:1) as a white solid (0.24 g, 51 % yield). IR (film): 3063, 3024, 2977, 2922, 2867, 1640, 1597, 1492, 1446, 1339, 1290, 1157, 1090, 1060, 997, 920, 889, 863, 813, 745, 694, 659, 587, 548 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.74 (m, 2H), 7.52 (m, 2H), 7.39 – 7.27 (m, 5H), 6.96 (s, 1H), 5.72 (m, 1H), 5.07 (m, 2H), 4.24 (s, 2H), 3.32 (m, 2H), 2.42 (s, 3H), 2.35 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 137.4, 135.1, 134.8, 130.6, 129.9, 129.2, 128.5, 128.4, 127.6, 121.1, 117.5, 57.6, 48.1, 33.2, 21.7. HRMS (EI) calcd for $C_{20}H_{22}BrNO_2S$: 419.0555. Found 339.9800 [M-Br].

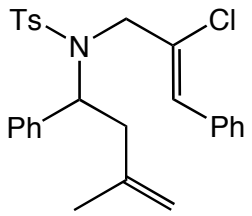


N-(1-Phenyl-but-3-enyl)-N-((*Z*)-3-phenyl-2-bromo-2-propenyl) - *p*-toluensulfonamide (13). Following the procedure described for compound **7** and starting from N-(1-Phenyl-but-3-enyl)-*p*-toluensulfonamide (0.19 g, 0.60 mmol), (*Z*)-(2,3-Dibromoprop-1-enyl)-benzene (0.20 g, 0.72 mmol), NaH (0.03 g, 0.66 mmol) and DMF (5 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 20:1) as a white solid (0.18 g, 59 % yield). IR (film): 3061, 3030, 2920, 2853, 1658, 1596, 1494, 1450, 1350, 1332, 1160, 1095, 1069, 988, 970, 944,

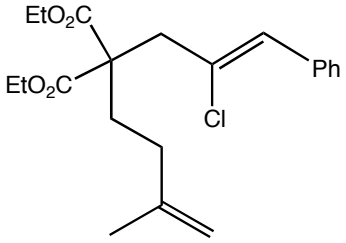
915, 886, 814, 776, 756, 728, 697, 666, 642, 558 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.4-7.2 (m, 12H), 6.69 (s, 1H), 5.61 (m, 1H), 5.15 (m, 1H), 4.98 (m, 2H), 4.23 (d, *J* =17.5 Hz, 1H), 3.96 (d, *J* = 17.5 Hz, 1H), 2.91 (m, 1H), 2.64 (m, 1H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 138.2, 137.1, 135.3, 134.6, 130.1, 129.8, 129.10, 129.07, 128.7, 128.5, 128.2, 127.8, 122.2, 118.0, 61.39, 53.9, 36.3, 21.7. HRMS (EI) calcd for $C_{26}H_{26}BrNO_2S$: 495.0868. Found 518.07584 [M+Na].



N-(1-Phenyl-but-3-enyl)-N-((*Z*)-3-phenyl-2-chloro-2-propenyl) - *p*-Toluensulfonamide (14): Following the procedure described for compound **7** and starting from N-(1-Phenyl-but-3-enyl)-*p*-toluensulfonamide[31] (0.20 g, 0.66 mmol), **III** (0.18 g, 0.80 mmol), NaH (0.03 g, 0.73 mmol) and DMF (5 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 10:1) as a white solid (0.22 g, 75 % yield). IR (film): 3065, 3030, 2976, 2922, 1641, 1597, 1493, 1448, 1337, 1304, 1184, 1158, 1119, 1090, 1059, 1016, 998, 954, 919, 895, 869, 813, 770, 754, 741, 696, 661, 608, 561, 544 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 7.3 Hz, 2H), 7.30 – 7.20 (m, 10H), 6.39 (s, 1H), 5.58 (m, 1H), 5.15 (m, 1H), 4.95 (m, 2H), 4.13 (d, *J* = 16.7 Hz, 1H), 3.79 (d, *J* = 16.7 Hz, 1H), 2.88 (m, 1H), 2.62 (m, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 138.1, 136.9, 134.5, 134.1, 129.6, 129.5, 129.10, 128.9, 128.5, 128.2, 128.1, 127.6, 127.2, 117.8, 61.0, 51.9, 36.0, 21.6. HRMS (ESI) calcd for $C_{26}H_{26}ClNO_2S$: 451.1373. Found 474.1264 [M+Na].

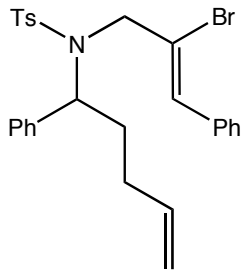


N-(1-Phenyl-3-methyl-but-3-enyl)-N-((*Z*)-3-phenyl-2-chloro-2-propenyl) - *p*-toluensulfonamide (15): Following the procedure described for compound **7** and starting from N-(1-Phenyl-3-methyl-but-3-enyl)-*p*-toluensulfonamide (0.30 g, 0.95 mmol), **III** (0.26 g, 1.14 mmol), NaH (0.05 g, 1.14 mmol) and DMF (10 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 9:1 to 5:1) as a white solid (0.21 g, 46 % yield). IR (film): 3065, 3030, 2976, 2922, 1641, 1597, 1493, 1448, 1337, 1304, 1184, 1158, 1119, 1090, 1059, 1016, 998, 954, 919, 895, 869, 813, 770, 754, 741, 696, 661, 608, 561, 544 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.37 (d, J = 7.3 Hz, 2H), 7.30 – 7.20 (m, 10H), 6.39 (s, 1H), 5.58 (m, 1H), 5.15 (m, 1H), 4.95 (m, 2H), 4.13 (d, *J* = 16.7 Hz, 1H), 3.79 (d, *J* = 16.7 Hz, 1H), 2.88 (m, 1H), 2.62 (m, 1H), 2.41 (s, 3H), 1.62 (3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 138.1, 136.9, 134.5, 134.1, 129.6, 129.5, 129.10, 128.9, 128.5, 128.2, 128.1, 127.6, 127.2, 117.8, 61.0, 51.9, 36.0, 21.6. HRMS (ESI) calcd for $C_{27}H_{28}ClNO_2S$: 465.1529. Found 488.1422 [M+Na].

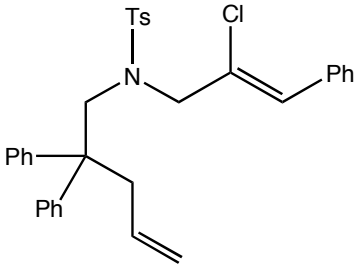


Diethyl-2-(3-methyl-but-3-enyl)-2'-((*Z*)-3-phenyl-2-chloro-2-propenyl) malonate (16): Following the procedure described for compound **7** and starting from diethyl-2-(3-methyl-But-3-enyl) malonate[32] (0.25 g, 1.09 mmol), **III** (0.30 g, 1.31 mmol), NaOEt (0.09 g, 1.01 mmol) and THF (10 ml) the desired product was obtained after silica gel chromatography (eluent: Hexane - CH_2Cl_2 1:1) as a transparent oil (0.40 g, 96 % yield). IR (film): 2979, 1732, 1447, 1257, 1232, 1196, 1181, 1096, 1030, 891,

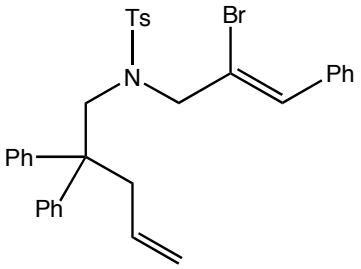
862, 752, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, J = 7.8 Hz, 2H), 7.38-7.24 (m, 3H), 6.52 (s, 1H), 4.71 (s, 1H), 4.22 (m, 4H), 3.22 (s, 2H), 2.18 (m, 2H), 1.95 (m, 2H), 1.71 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 144.9, 134.8, 129.3, 129.2, 129.1, 128.4, 128.1, 110.9, 61.7, 57.3, 43.2, 32.6, 30.2, 22.6, 14.3. HRMS (ESI) calcd for $C_{21}H_{27}ClO_4$: 378.1598. Found 401.8795 [M+Na].



N-(1-Phenyl-pent-4-enyl)-N-((*Z*)-3-phenyl-2-bromo-2-propenyl) - *p*-Toluensulfonamide (17): Following the procedure described for compound **7** and starting from N-(1-Phenyl-pent-3-enyl)-*p*-toluensulfonamide[33] (0.19 g, 0.60 mmol), (*Z*)-(2,3-Dibromoprop-1-enyl)-benzene (0.20 g, 0.72 mmol), NaH (0.03 g, 0.66 mmol) and DMF (10 ml) the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 20:1) as an oil (0.18 g, 59 % yield). IR (film): 3068, 3030, 2863, 1660, 1594, 1495, 1450, 1332, 1160, 1097, 1064, 988, 972, 944, 915, 886, 814, 778, 756, 731, 697, 667, 641, 559 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.37-7.15 (m, 12H), 6.69 (s, 1H), 5.72 (m, 1H), 5.07 (m, 1H), 4.92 (m, 2H), 4.21 (d, *J* = 16.4 Hz, 1H), 3.95 (d, *J* = 16.4 Hz, 1H), 2.40 (s, 3H), 2.30-1.70 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.4, 137.2, 135.4, 131.6, 129.9, 129.8, 129.7, 129.5, 129.0, 128.9, 128.8, 128.6, 128.4, 128.3, 128.2, 127.9, 127.8, 122.4, 115.7, 66.1, 61.0, 53.7, 31.1, 31.0, 21.7, 15.5. HRMS (ESI) calcd for $C_{27}H_{28}BrNO_2S$: 509.1024. Found 532.0922 [M+Na].

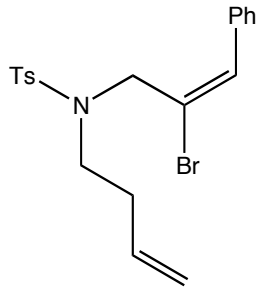


N-(1-Phenyl-but-3-enyl)-N-((*Z*)-3-phenyl-2-chloro-2-propenyl) - *p*-toluensulfonamide (18):): Following the procedure described for compound **14** and starting from N-(2,2'-diphenyl-pent-3-enyl)-*p*-toluensulfonamide[34] (0.30 g, 0.76 mmol), **3** (0.21 g, 0.91 mmol), NaH (0.03 g, 0.84 mmol) and DMF (10 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 9:1) as a white foam (0.31 g, 74 % yield). IR (film): 3060, 3025, 2924, 1598, 1493, 1445, 1344, 1159, 1089, 921, 813, 742, 699, 655, 551 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.18 (m, 17H), 6.12 (s, 1H), 5.58 (m, 1H), 4.90 (m, 2H), 4.22 (s, 2H), 3.30 (s, 2H), 3.12 (d, *J* = 6.9 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.6, 143.6, 137.6, 134.7, 134.0, 129.7, 129.3, 129.0, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 126.8, 118.1, 57.0, 55.7, 51.2, 41.7, 21.7. HRMS (ESI) calcd for $C_{33}H_{32}ClNO_2S$: 541.1842. Found 564.1731 [M+Na].

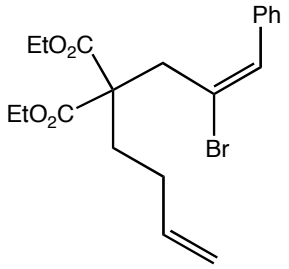


N-(1-Phenyl-but-3-enyl)-N-((*Z*)-3-phenyl-2-bromo-2-propenyl) - *p*-toluensulfonamide (19). Following the procedure described for compound **14** and starting from N-(2,2'-diphenyl-pent-3-enyl)-*p*-toluensulfonamide (0.30 g, 0.76 mmol), (*Z*)-(2,3-Dibromoprop-1-enyl)-benzene (0.25 g, 0.91 mmol), NaH (0.04 g, 0.91 mmol) and DMF (10 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 10:1) as a white foam (0.27 g, 60 % yield). IR (film): 3059,

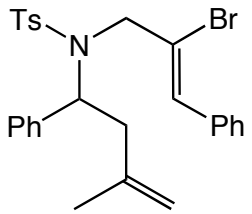
3024, 2930, 1598, 1490, 1446, 1340, 1156, 913, 812, 736, 697, 656, 548 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.18 (m, 17H), 6.44 (s, 1H), 5.58 (m, 1H), 4.90 (m, 2H), 4.27 (s, 2H), 3.42 (s, 2H), 3.12 (d, *J* = 7.0 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.6, 143.7, 137.5, 135.0, 134.7, 130.2, 129.8, 129.1, 128.2, 128.1, 127.9, 126.8, 120.3, 118.2, 57.4, 57.3, 51.2, 41.7, 21.7. HRMS (ESI) calcd for $C_{33}H_{32}BrNO_2S$: 585.1337. Found 608.1209 [M+Na].



N-(But-3-enyl)-N-((*E*)-3-phenyl-2-bromo-2-propenyl) - *p*-toluensulfonamide (20): Following the procedure described for compound **7** and starting from N-(But-3-enyl)-*p*-toluensulfonamide (0.19 g, 0.84 mmol), **IV** (0.28 g, 1.01 mmol), NaH (0.04 g, 1.01 mmol) and DMF (10 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 10:1) as an oil (0.34 g, 97 % yield). IR (film): 3059, 3026, 2976, 2924, 1641, 1597, 1494, 1445, 1341, 1304, 1158, 1090, 1032, 918, 814, 748, 701, 670, 657, 591, 553 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (m, 2H), 7.40- 7.29 (m, 3H), 7.25 (m, 3H), 7.17 (m, 2H), 5.48 (m, 1H), 4.72 (m, 2H), 4.32 (s, 2H), 3.12 (m, 2H), 2.41 (s, 3H), 1.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.5, 137.6, 137.4, 135.6, 134.8, 129.7, 128.9, 128.6, 128.3, 127.7, 124.6, 117.1, 49.2, 46.5, 32.5, 21.7. HRMS (EI) calcd for $C_{20}H_{22}BrO_4$: 419.0555. Found 442.0456 [M+Na].



Diethyl-2-(but-2-enyl)-2'-((*E*)-3-phenyl-2-bromo-2-propenyl) malonate (21): Following the procedure described for compound **5** and starting from diethyl-2-(But-3-enyl) malonate (0.18 g, 0.84 mmol), **IV** (0.30 g, 1.09 mmol), NaOEt (0.07 g, 1.01 mmol) and THF (10 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 20:1) as a transparent oil (0.31 g, 91 % yield). IR (film): 2981, 1730, 1642, 1623, 1445, 1366, 1269, 1184, 1078, 1032, 913, 861, 754, 700, 553 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38 (m, 2H), 7.33-7.25 (m, 3H), 7.20 (s, 1H), 5.56 (m, 1H), 4.85 (m, 1H), 4.77 (m, 1H), 4.22 (m, 4H), 3.54 (s, 2H), 2.00 (m, 2H), 1.44 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 137.5, 137.2, 136.1, 128.9, 128.5, 127.9, 126.5, 114.9, 61.7, 57.1, 37.1, 30.6, 28.3, 14.11. HRMS (ESI) calcd for $C_{19}H_{23}BrO_4$: 408.0936. Found 431.0826 [M+Na].

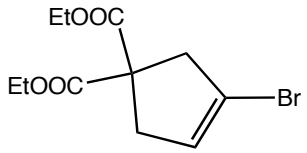


N-(1-Phenyl-3-methyl-but-3-enyl)-N-((*Z*)-3-phenyl-2-bromo-2-propenyl) - *p*-toluensulfonamide (22): Following the procedure described for compound **7** and starting from N-(1-Phenyl-3-methyl-but-3-enyl)-*p*-toluensulfonamide (0.30 g, 0.95 mmol), (*Z*)-(2,3-Dibromoprop-1-enyl)-benzene (0.34 g, 1.23 mmol), NaH (0.05 g, 1.23 mmol) and DMF (10 ml) the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 20:1 to 10:1) as a white solid (0.18 g, 37 % yield). IR (film): 3061, 3030, 2975, 2924, 1649, 1597, 1493, 1446, 1338, 1304, 1157, 1091, 1063, 1016, 920, 894, 813, 770, 740, 696, 660, 608, 572, 549 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.19 (m, 12H), 6.65 (s, 1H), 5.32 (m, 1H), 4.7 (s, 1H), 4.62 (s, 1H), 4.22 (d, *J* = 16.8 Hz, 1H), 4.00 (d, *J* = 16.8 Hz, 1H), 2.95 (m, 1H), 2.50 (m, 1H), 2.41 (s, 3H), 1.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 141.4, 138.2, 137.1, 135.4, 129.9, 129.8, 129.1, 129.0, 128.6, 128.4, 128.2, 128.1, 127.9, 127.7, 122.2, 114.0, 59.7, 53.8, 40.0, 22.7, 21.7. HRMS (ESI) calcd for $C_{27}H_{28}BrNO_2S$: 509.1024. Found 532.0925 [M+Na].

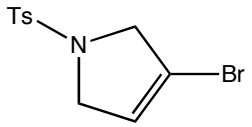
Experimental section: characterization of products

General procedure for ring closing metathesis:

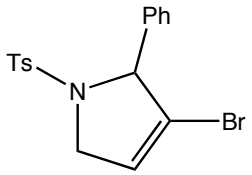
A screw cap vial with septum was charged in a glove box with the catalyst. Solvent was then added and the mixture was stirred until complete dissolution. The vial was then closed and placed in an oil bath pre-heated to 65 degree outside of the box (It seems to be important from the collected data to pre-heat the catalyst solution before mixing it with the desired substrate). After 2 minutes a solution of the desired diene was added with a syringe. The mixture was stirred until from TLC and/or GC-MS analysis the reaction was complete. The vial was then cooled to room temperature and opened to the air for few minutes to completely decompose the catalyst. The resulting yellow-brown solution was directly charged on the top of a silica gel filter for purification.



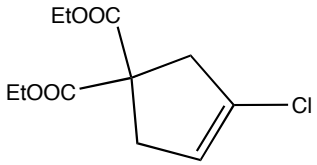
3-Bromo-1,1'-(dicarboxilic acid diethyl ester)-cyclopent-3-ene (5a): Following the general procedure and starting from **9** (0.063 g, 0.16 mmol), **GII** (0.0027 mg, 0.0032 mmol), and benzene (1.6 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 20:1) as a colorless oil (0.041 g, 87 % yield). IR (film): 2981, 2937, 1730, 1630, 1464, 1445, 1389, 1366, 1257, 1242, 1180, 1160, 1096, 1073, 1058, 1034, 1013, 981, 861, 820 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.71 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 4H), 3.21 (m, 2H), 2.96 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.2, 128.3, 117.0, 62.2, 58.9, 46.7, 40.8, 14.2. HRMS (EI) calcd for $C_{11}H_{13}BrO4$: 290.0154. Found 313.0048 [M+Na].



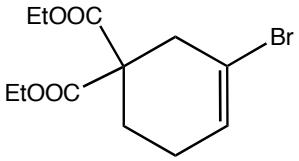
1-Tosyl-2,5-dehydro-3-bromopyrrole (7a): Following the general procedure and starting from **7** (0.063 g, 0.16 mmol), **GII** (0.0027 g, 0.0032 mmol), and benzene (1.6 ml), the desired product was obtained after silica gel chromatography (eluent: Toluene; with *p*-anisaldehyde the product gave yellow spots on TLC; the main impurity gave black spots) as a white crystalline solid (0.029 g, 64 % yield). From MS analysis the main impurity arises from cross metathesis of **7** with the styrene generated during the reaction. IR (film): 2915, 2864, 1632, 1599, 1348, 1324, 1162, 1102, 1048, 817, 667, 601, 545 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 5.80 (m, 1H), 4.10 (m, 4H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.2, 134.0, 130.2, 127.7, 125.9, 114.1, 58.8, 55.4, 21.8. HRMS (ESI) calcd for $C_{11}H_{12}BrNO_2S$: 300.9772. Found 323.9643 [M+Na].



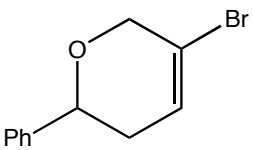
1-Tosyl-2,5-dehydro-2Phenyl-3-bromopyrrole (8a): Following the general procedure and starting from **8** (0.085 g, 0.18 mmol), **GII** (0.0027 g, 0.0032 mmol), and benzene (1.8 ml), the desired product was obtained after silica gel chromatography (eluent: Toluene) as a white crystalline solid (0.051 g, 76 % yield). From NMR and MS analysis the main impurity arise from cross metathesis of **8** with the styrene generated during the reaction. IR (film): 3030, 2920, 2871, 1630, 1598, 1493, 1455, 1348, 1162, 1094, 1044, 827, 814, 755, 698, 670, 604, 576, 546 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.32-7.21 (m, 5H), 6.02 (s, 1H), 5.40 (m, 1H), 4.35 (m, 1H), 4.23 (m, 1H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 138.3, 135.5, 129.7, 128.7, 128.6, 128.2, 127.5, 125.6, 119.9, 55.2, 21.7. HRMS (ESI) calcd for $C_{17}H_{16}BrNO_2S$: 377.0085. Found 399.9984 [M+Na].



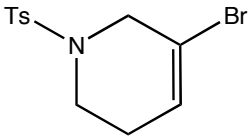
3-Chloro-1,1'-(dicarboxilic acid diethyl ester)-cyclopent-3-ene (9a): Following the general procedure and starting from **9** (0.056 g, 0.16 mmol), **GII** (0.0027 mg, 0.0032 mmol), and benzene (1.6 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 20:1) as a colorless oil (0.038 g, 96 % yield). The analytical data matched the one previously reported in literature.[35]



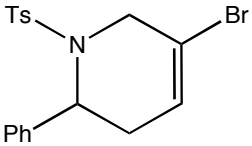
3-Bromo-1,1'-(dicarboxilic acid diethyl ester)-cyclohex-3-ene (10a): Following the general procedure and starting from **10** (0.065 g, 0.16 mmol), **GII** (0.0027 g, 0.0032 mmol), and benzene (1.6 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 20:1) as a colorless oil (0.048 g, 96 % yield). IR (film): 2980, 2937, 2846, 1730, 1655, 1464, 1445, 1389, 1366, 1335, 1305, 1277, 1246, 1230, 1214, 1175, 1135, 1086, 1069, 1053, 1016, 976, 949, 897, 859, 838, 768, 733, 696 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.01 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 4H), 2.93 (s, 2H), 2.13 (m, 4H), 1.23 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 127.8, 118.5, 61.9, 55.1, 39.5, 26.4, 24.6, 14.2. HRMS (ESI) calcd for $C_{12}H_{17}BrO4$: 304.0310. Found 327.0202 [M+Na].



2-Phenyl-5-bromo-3,6-dihydro-pyran (11a): Following the general procedure and starting from **11** (0.055 g, 0.16 mmol), **GII** (0.0027 g, 0.0032 mmol), and benzene (1.6 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - CH_2Cl_2 7:1) as a colorless oil (0.036 g, 94 % yield). IR (film): 3062, 3031, 2928, 2897, 2833, 1655, 1494, 1450, 1426, 1366, 1271, 1235, 1092, 1024, 1011, 982, 960, 905, 876, 821, 756, 697, 532 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 5.80 (m, 1H), 4.10 (m, 4H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 141.3, 128.7, 128.1, 126.2, 126.1, 119.6, 75.4, 70.9, 35.5. HRMS (EI) calcd for $C_{11}H_{11}BrO$: 237.9993. Found 237.9996.

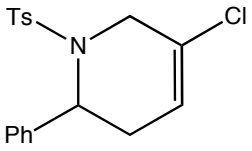


1-Tosyl-1,2,3,6-tetrahydro-5-bromopyridine (12a): Following the general procedure and starting from **12** (0.085 g, 0.18 mmol), **GII** (0.0027 g, 0.0032 mmol), and benzene (1.6 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane – Et_2O 9:1) as a white crystalline solid (0.048 g, 96 % yield). IR (film): 2923, 2846, 2359, 2340, 1336, 1165, 1098, 1010, 970, 945, 817, 731, 652, 570, 548 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 6.06 (m, 1H), 3.78 (s, 2H), 3.22 (t, *J* = 5.7 Hz, 2H), 2.44 (s, 3H), 2.25 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.1, 133.8, 130.1, 127.8, 127.1, 115.9, 51.0, 42.0, 27.4, 21.8. HRMS (EI) calcd for $C_{12}H_{14}BrNO_2S$: 314.9929. Found 337.9801[M+Na].

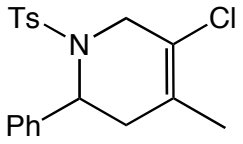


1-Tosyl-1,2,5,6-tetrahydro-2-phenyl-5-bromopyridine (13a): Following the general procedure and starting from **13** (0.080 g, 0.16 mmol), **GII** (0.0027 g, 0.0032 mmol),

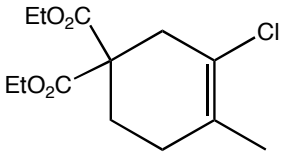
and benzene (1.6 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane – Et_2O 6:1) as a colorless oil (0.060 g, 95 % yield). Due to the low solubility of **13** in benzene for this reaction it is important to heat the starting substrate solution to 60 °C before injecting it into the catalyst mixture. IR (film): 3061, 3030, 2920, 2853, 1658, 1598, 1494, 1450, 1439, 1350, 1332, 1159, 1095, 1069, 988, 943, 886, 814, 776, 756, 727, 697, 666, 642, 575, 558 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.30 (m, 7H), 6.05 (m, 1H), 5.28 (d, *J* = 5.5 Hz, 1H), 4.31 (d, *J* = 19.4 Hz, 1H), 3.49 (m, 1H), 2.60-2.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 138.1, 137.5, 130.0, 128.8, 128.1, 127.5, 127.3, 125.6, 117.01, 52.3, 46.7, 28.5, 21.8. HRMS (EI) calcd for $C_{18}H_{18}BrNO_2S$: 391.0242. Found 414.0136 [M+Na].



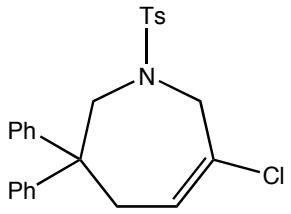
1-Tosyl-1,2,5,6-tetrahydro-2-phenyl-5-bromopyridine (14a): Following the general procedure and starting from **14** (0.072 g, 0.16 mmol), **GII** (0.0027 g, 0.0032 mmol), and benzene (1.6 ml) the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 9:1) as a colorless oil (0.054 g, 97 % yield). Due to the low solubility of **14** in benzene for this reaction it is important to heat the starting substrate solution to 60 °C before injecting it into the catalyst mixture. IR (film): 3062, 3032, 2923, 2851, 1661, 1595, 1494, 1450, 1439, 1334, 1305, 1160, 1096, 1068, 1005, 974, 948, 915, 888, 814, 784, 759, 734, 698, 671, 644, 584, 560, 539, 402 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.30 (m, 7H), 5.81 (m, 1H), 5.25 (d, *J* = 5.5 Hz, 1H), 4.20 (d, *J* = 18.4 Hz, 1H), 3.40 (m, 1H), 2.60-2.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.6, 137.9, 137.2, 129.8, 128.6, 127.9, 127.3, 127.2, 127.0, 121.3, 52.2, 44.9, 26.9, 21.6. HRMS (ESI) calcd for $C_{18}H_{18}ClNO_2S$: 347.0747. Found 370.0637 [M+Na].



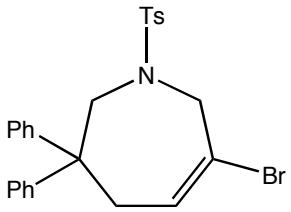
1-Tosyl-1,2,5,6-tetrahydro-2-phenyl-5-bromopyridine (15a): Following the general procedure and starting from **15** (0.075 g, 0.16 mmol), **GII** (0.0068 g, 0.008 mmol), and CH_2Cl_2 (1.6 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 10:1 to Hexane - Et_2O 4:1) as a colorless oil (0.047 g, 81 % yield). Due to the low solubility of **15** in benzene for this reaction it is important to heat the starting substrate solution to 60 °C before injecting it into the catalyst mixture. The same reaction performed using benzene as a solvent gave lower yield. IR (film): 2919, 2856, 1683, 1596, 1495, 1447, 1338, 1162, 1119, 1089, 1055, 812, 772, 738, 690, 646, 558 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.30 (m, 7H), 5.24 (d, *J* = 4.3 Hz, 1H), 4.15 (d, *J* = 18 Hz, 1H), 3.40 (m, 1H), 2.40 (m, 5H), 1.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.8, 138.4, 137.4, 129.8, 128.8, 128.1, 127.4, 127.3, 127.1, 121.2, 53.5, 45.4, 32.8, 21.8, 19.4. HRMS (ESI) calcd for $C_{19}H_{20}ClNO_2S$: 361.0903. Found 384.0796 [M+Na].



3-Chloro-4-methyl-1,1'-(dicarboxilic acid diethyl ester)-cyclohex-3-ene (16a): Following the general procedure and starting from **16** (0.054 g, 0.14 mmol), **GII** (0.006 g, 0.0071 mmol), and CH_2Cl_2 (1.4 ml), the desired product was obtained after silica gel chromatography (eluent: Hexane - Et_2O 20:1) as a colorless oil (0.036 g, 92 % yield). IR (film): 2979, 1730, 1443, 1367, 1295, 1252, 1240, 1178, 1114, 1091, 1057, 1028, 861, 816 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.19 (q, J = 7.2 Hz, 4H), 2.83 (s, 2H), 2.12 (s, 4H), 1.76 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 128.6, 122.9, 61.8, 54.8, 38.1, 29.1, 27.7, 19.8, 14.2. HRMS (ESI) calcd for $C_{19}H_{13}ClO4$: 274.0972. Found 297.0781 [M+Na].



1-Tosyl-2,3,4,7-tetrahydro-3,3-diphenyl-5-chloro-azepine (18a): Following the general procedure and starting from **18** (0.077 g, 0.141 mmol), **GII** (0.0060 g, 0.007 mmol), and CH_2Cl_2 (14 ml), the desired product was obtained after silica gel chromatography (eluent: Toluene) as a white solid (0.046 g, 76 % yield). The same reaction performed using benzene as a solvent gave a slightly lower yield. IR (film): 2920, 1597, 1495, 1444, 1669, 1160, 1091, 912, 813, 753, 700, 657, 565, 547 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, J = 8.2 Hz, 2H), 7.32-7.20 (m, 12H), 5.87 (t, J = 8.0 Hz, 1H), 4.30 (s, 2H), 3.97 (s, 2H), 3.05 (d, J = 6.8 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4, 144.0, 134.9, 130.1, 129.2, 128.6, 127.7, 127.4, 126.8, 59.4, 55.3, 51.6, 36.5, 21.8. HRMS (ESI) calcd for $C_{25}H_{24}ClNO_2S$: 437.1216. Found 460.1110 [M+Na].



1-Tosyl-2,3,4,7-tetrahydro-3,3-diphenyl-5-bromo-azepine (19a): Following the general procedure and starting from **19** (0.083 g, 0.14 mmol), **GII** (0.0060 g, 0.007 mmol), and CH_2Cl_2 (14 ml), the desired product was obtained after silica gel chromatography (eluent: Toluene) as a white foam (0.046 g, 67 % yield). IR (film): 2921, 1597, 1494, 1445, 1669, 1159, 1092, 907, 813, 804, 784, 759, 733, 700, 659, 565, 547 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.35-7.20 (m, 12H), 6.10 (t, *J* = 8.0 Hz, 1H), 4.05 (m, 2H), 3.03 (d, *J* = 6.8 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 146.4, 144.0, 134.9, 131.7, 130.0, 129.3, 128.9, 128.5, 128.3, 127.7, 127.6, 26.8, 118.5, 59.3, 57.1, 51.6, 38.0, 21.8. HRMS (ESI) calcd for $C_{25}H_{24}BrNO_2S$: 481.0711. Found 504.0583 [M+Na].

4.2 References:

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[4] (a) Chao, W.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2505. (b) Chao, W.; Meketa, M. L.; Weinreb, S. M. *Synthesis* **2004**, *12*, 2058. (c) White, D. E.; Stewart, I. C.; Grubbs, R. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 810. (d) White, D. E.; Stewart, I. C.; Seashore-Lodlow, B. A.; Grubbs, R. H.; Stoltz, B. M. *Tetrahedron* **2010**, *66*, 4668. This paper indeed indicates that related structures to the one reported in ref 4c cannot be obtained via RCM of the corresponding alkenyl chloride substrates.

[5] For Grubbs II (**GII**), see ref 4a and b. For Schrock and Grubbs I (**GI**), see: Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

[6] For recent efforts to use alkenyl halides in CM, see: (a) Sashuk, V.; Samojlowicz, C.; Szadkowska, A.; Grela, K. *Chem. Commun.* **2008**, 2468. (b) Macnaughtan, M. L.;

Gary, J. B.; Gerlach, D. L.; Johnson, M. J. A.; Kampf, J. W. *Organometallics* **2009**, *28*, 2880.

[7] See the Supporting Information for details.

[8] The identity of the counterion (Br- or Cl-) was established through comparison of the ^{1}H NMR signal of the imidazolinium proton with authentic samples of SIMes·HCl and SIMes·HBr recorded in $CDCl_3$ at the same concentration. See the Supporting Information for spectra.

[9] To our knowledge, this is the first example where a second-generation ruthenium catalyst decomposes via formal loss of the NHC ligand. For other decomposition pathways, see: (a) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev*. **2009**, *109*, 3708. (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev*. **2010**, *110*, 1746, and references cited.

[10] It is commonly assumed that alkenyl halides react very rapidly with the ruthenium center, giving rise to Fischer-type carbene moieties; see discussion in ref 4a and: Macnaughtan, M. L.; Johnson, M. J. A.; Kampf, J. W. *J. Am. Chem. Soc.* **2007**, *129*, 7708.

[11] In a separate experiment, we made sure that compound **2** does not react with an equimolar amount of tricyclohexylphosphine. This excludes a reaction scenario where the phosphine liberated from **GII** during the initial CM of **1** attacks the bromoalkene via elimination of HBr.

[12] Terminal substitution has been successfully used in the past to minimize unwanted secondary metathesis activity during RCM. For the first example, see: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. For more recent, selected examples where the geometry of a terminal phenyl or methyl group affects reaction yields, see: (b) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904. (c) Rölle, T.; Grubbs, R. H. *Chem. Commun.* **2002**, 1070. (d) Stenne, B.; Timperio, J.; Savoie, J.; Dudding, T.; Collins, S. K. *Org. Lett.* **2010**, *12*, 2032.

[13] This strategy would also generate, after each catalytic cycle, a propagating species more stable than a methylidene. For a discussion regarding the advantages of a stable propagating species in solution, see ref 12b.

[14] The main byproduct was unreacted starting material.

[15] Screening of reaction conditions (solvents, precatalysts etc.) can be found in the Supporting Information.

[16] Reference 4d reports a 24% yield of **16a** starting from the non-phenylated malonate derivative of **16** when employing 5 mol % of an optimized second-generation ruthenium precatalyst.

[17] In these cases, the approach of the alkenyl bromide seems to be more difficult resulting in lower activity. For an early example on the Thorpe-Ingold effect in RCM, see: Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.

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2010	" C_2-Symmetric Chiral Disulfoxide Ligands in Rhodium-Catalyzed 1,4-Addition: From Ligand Synthesis to the Enantioselection Pathway". Mariz, R.; Poater, A.; Gatti, M.;

Drinkel, E.; Bürgi, J. J.; Luan, X.; Blumentritt, S.; Linden, A.; Cavallo, L.; Dorta, R. *Chem. Eur. J.* **2010**, published online.

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